Multimodal deficits in right brain damaged patients with and without neglect and their modulation by sensory stimulation techniques

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Abstract

Spatial neglect is a neurological disorder most often caused by vascular, right hemispheric brain damage. It is mainly characterized by a failure to attend, orient to or react to stimuli presented in the contralesional hemispace. By definition, neglect is seen as a higher order spatial disorder not merely caused by a sensory (e.g. hemianopia) or motor (e.g. hemiplegia) deficit. This definition includes the aspect of multimodality, which plays a central role in the assessment and therapy of the syndrome. Neglect may affect any sensory modality (visual, auditory, olfactory, tactile) or motor as well as representational aspects, leading to deficits in daily life, such as spatial orientation and navigation, visual exploration or auditory localization. Several studies in the last decade addressed the assessment and modulation of those neglect associated deficits using sensory, bottom-up stimulation techniques like galvanic vestibular stimulation or neck-proprioceptive stimulation (e.g. varying head-on-trunk-orientation), which are regarded as promising techniques to ameliorate the syndrome. Interestingly, in these studies, it was observed that not only neglect patients, but also right brain damaged patients *without* spatial neglect, serving as patient control groups have peculiarities in performing those tasks, and show associations (e.g. disorganized search strategies) as well as dissociations (e.g. non-lateralized exploration behavior) compared to neglect patients.

The present doctoral thesis addressed the aspect of multimodality for the visual, auditory and tactile domain concerning exploration as well as localization and identification. In both studies, visual neglect screening tests were used to assign right brain damaged patients to any of the two patient subgroups (right brain damaged controls vs. neglect patients).

In **study 1**, visual and tactile exploration behavior was analyzed using the same task for both modalities, allowing a direct comparison of search patterns concerning omissions and perseverations (repetitive search) as well as their modulation by galvanic vestibular stimulation. Subjects were instructed to name 96 stimuli on a large exploration board either with (visual condition: each of the 96 stimuli had to be named by terms of shape and attached) or without

(tactile condition: blindfolded subjects were asked to name each stimulus' shape by only using the ipsilesional, i.e. right hand) the help of vision.

The typical neglect associated lateralization bias (left-right-gradient) in exploration was found in both modalities in neglect patients, with higher omission rates in the left compared to the right hemispace of the search board in both tasks (visual and tactile), even if that difference of leftward vs. rightward attention bias did not reach a significant statistical level. No such gradient was found in right brain damaged controls. A similar pattern was found for perseveration rates in neglect patients, showing a rightward bias in repeated search, whereas right brain damaged controls showed similar repetition rates in their search in both hemifields.

Interestingly, right brain damaged patients without neglect also showed deficits in exploration behavior compared to healthy controls. They showed omission rates in the left and right hemispace in the visual task as well as in the left hemispace of the tactile task, which scored between those of neglect patients and healthy controls. In the right hemispace of the tactile task, they even performed on the same level as neglect patients. Perseveration rates were even higher in the left hemispace compared to neglect patients, while both patient groups showed similar perseveration rates in the left hemispace. Notably, all three subject groups, including the healthy controls, showed a similar, high level of perseverations in the tactile task across the whole exploration board.

In the present study 1, galvanic vestibular stimulation did not have any clear ameliorating effect on the exploration performance.

The results are discussed with respect to recent literature on the basis of the assumption of a multimodal representation of space, which seems to be impaired in right brain damaged patients with and without neglect in various degrees.

Study 2 investigated the characteristics of auditory neglect concerning auditory localization and identification performance and its modulation by passive head-on-trunk-rotation (passive head rotation 20° left vs. straight vs. 20° right, the trunk remained in straight position in all conditions) as a form of neck-proprioceptive sensory stimulation. Similarly to the visual system, the auditory system is assumed to be organized in two main processing paths, namely a dorsal ("where" and "how") and a ventral ("what") stream providing different auditory functions. While localization seems to be realized by the dorsal auditory processing stream, identification tasks are assumed to be processed preferentially in the ventral stream.

In the first task (experiment 2a), subjects' auditory subjective median plane (ASMP) was measured for sound locations in the horizontal plane presented via headphones using binaural sound parameters derived by head related transfer functions (HRTF), simulating a sum of 37 sound locations with 90° to le left and right from the subjective midline of the subject in azimuth (=the horizontal plane). While there was a right sided shift of the ASMP observable in head straight and head right conditions in those patients with left neglect, passive leftward head rotation led to a significant shift of the ASMP to the left, resulting in a relocation of the ASMP and transient amelioration of auditory neglect.

Furthermore, that ameliorating effect of passive head rotation was also observable in the second task which was an auditory identification task. Subjects were asked to perform a same-different task using pairs of monosyllabic words presented in a left (-90°, -30°), a central (-30°, +30°), or a right space sector (+30°, +90°) in the horizontal plane. As in experiment 2a sounds were monosyllabic words. Their spatial position in the horizontal plane was manipulated by using the directional dependent head-related transfer functions (HRTF) for these different spatial positions. The final sounds were monosyllabic words with a definite spatial position in azimuth, and were delivered via headphones. Although sound localization did not have to be explicitly computed by the subjects, it did affect the performance in the identification task: the proportion of correctly identified word pairs followed a left-to-right gradient with highest proportions of correct identifications in the right (ipsilesional) sector in the neglect group. Interestingly, passive head rotation to the left – with unchanged auditory input via headphones - significantly increased the proportions of correct word pair identifications in the left and mid spatial position of the tasks, selectively in the group of neglect patients. These results are also discussed with respect to current literature and on the basis of the assumption of the two auditory processing streams mentioned above.

The results of both studies indicate four aspects, which are discussed in more detail with respect to current literature: a) visual neglect screening tests seem to be suitable to identify neglect patients with multimodal neglect associated deficits; b) space coding may be realized with a higher order, multimodal representation of space, which seems to be impaired in right brain damaged patients with and without neglect; c) exploration deficits in right brain damaged patients, namely omissions and repetitive search behavior, seem to deflect two distinct phenomena affecting right brain damaged patients; and d) sensory, bottom-up stimulation techniques are suitable to ameliorate multimodal neglect even in a crossmodal way.

In sum, the present doctoral thesis brings new insights towards the exploration and localization performance of right brain damaged patients with and without neglect and their modulation using sensory, bottom-up treatments, which need to be replicated and extended by future studies.

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Abbreviations

AE:	aftereffect
A1:	primary auditory cortex
ASMP:	auditory subjective median plane
Base-Pre-CL:	baseline prior to GVS-CL
Base-Pre-CR:	baseline prior to GVS-CR
BG:	basal ganglia
CE:	capsula externa
CI:	capsula interna
Controls:	healthy controls' subgroup
CVE:	cerebrovascular event
CVS:	caloric vestibular stimulation
FEF:	frontal eye field
fMRI:	functional magnetic resonance imaging
General Base:	general baseline
GVS:	galvanic vestibular stimulation
GVS-CL:	left-cathodal/right-anodal galvanic vestibular stimulation
GVS-CR:	left-anodal/right-cathodal galvanic vestibular stimulation
GVS-Sham:	Sham-/Placebo galvanic vestibular stimulation
HH:	homonymous hemianopia
HRTF:	head related transfer function
ICB:	intracerebral bleeding
ISC:	ischemic brain damage
ITD diotic task:	interaural time difference diotic task
MCI:	middle cerebral artery infarction
MIP:	medial intraparietal area
N+:	neglect patients' subgroup
NMV:	neck muscle vibration
OKS:	optokinetic stimulation
PA:	prism adaptation

PCI:	posterior cerebral artery infarction
PIVC:	parieto-insular vestibular cortex
PPC:	posterior parietal cortex
RBD:	right brain damaged controls' subgroup
STG:	superior temporal gyrus
tDCS:	transcranial direct current stimulation
TENS:	transcutaneous electric nerve stimulation
Thal:	Thalamus
TMS:	transcranial magnetic stimulation
TSL:	time since lesion
VIP:	ventral intraparietal area
VOR:	vestibulo-ocular reflex
VSR:	vestibulo-spinal reflex

Introduction

Neglect is formally defined as a neurological disorder, in which patients fail to attend, respond or orient to sensory stimuli in the contralesional, i.e. left hemispace. By definition, it is not merely caused by sensory (e.g. hemianopia) or motor (e.g. hemiplegia) deficits (Kerkhoff, 2001; Karnath, 2012). This description is not at all sufficient to depict the complexity of this phenomenon. The clinically observable consequences are affecting almost every part of the patients' daily life, e.g. reading, responding to other people or navigating even in their familiar environment.
Due to the latter fact, lots of studies evaluated the effectiveness of different neglect treatments. Current established interventions are capable to compensate neglect associated deficits partly and temporarily. Nevertheless, there is a constant need of new treatments which are able to reduce patients' deficits in a longer lasting way and improve their ability to act more autonomously in daily life in terms of activities and participation (Kerkhoff & Schenk, 2012).

In the present dissertation, aspects of multimodal deficits in patients suffering from left spatial neglect after right brain damage and patients with a similar brain damage but without spatial neglect were investigated. This crucial issue plays an important role given that neglect phenomena often affect multiple modalities, such as visual, auditory or tactile, separately or even simultaneously (Kerkhoff, 2001). Hence, the present experiments concern different subtypes of neglect phenomena and associated deficits after right brain damage and their modulation by sensory stimulation techniques.

1 Clinical neglect signs and subtypes

Neglect designates a complex neurological disorder defined as a failure to "react to or process sensory stimuli" presented in the contralesional hemispace after left or right brain damage (Kerkhoff, 2001). Yet, there is a growing interest in ipsilesional neglect phenomena associated with right frontal and subcortical lesions (Sacchetti, Goedert, Foundas, & Barrett, 2015). Though incidence rates for neglect after infarction of the middle cerebral artery are initially similar in acute stroke after left and right hemispheric stroke (62% vs. 72% according to Stone et al., 1991; 20% vs. 43% according to Ringman, Saver, Woolson, Clarke, & Adams, 2004), there is some evidence that neglect severity and persistence seem to be moderated by age older than 65 (Gottesman et al., 2008; Stone, Halligan, & Greenwood, 1993), and laterality of brain damage (Stone et al., 1991; Ringman, Saver, Woolson, Clarke, & Adams, 2004; Stone, Patel, Greenwood, & Halligan, 1992; Suchan, Rorden, & Karnath, 2012), while the latter fact is discussed controversially with respect to severity. Note that incidence appraisal in case of right vs. left sided brain damage should be interpreted with caution due to possible assessment difficulties in left sided stroke patients caused by concurrent deficits in language processing (Stone et al., 1993).

As already mentioned above, multimodal deficits in neglect are by definition neither due to an elementary sensory or motor defect, e.g. caused by deafferentation, nor to any cognitive or emotional disorder, e.g. depression (Kerkhoff, 2001).

The aforementioned definition entails a crucial characteristic of neglect, concerning its multimodal or multisensory nature (Jacobs, Brozzoli, & Farne, 2012). It may affect *sensory* (visual, tactile, auditory, olfactory) as well as *motor* (reduced use of contralateral extremities) or *representational* (imagination of space) aspects. As recently reviewed by Jacobs and colleagues (Jacobs et al., 2012), these modalities may be affected and spared separately, though multimodal deficits are present in the majority of neglect patients. Several subtypes of neglect have been reported in the past years, which revealed dissociations (Buxbaum et al., 2004; Vallar, Bottini, Sterzi, Passerini, & Rusconi, 1991) as well as co-incidence (Kerkhoff, 1999; Schindler, Clavagnier, Karnath, Derex, & Perenin, 2006) of neglect in different modalities and subtypes (the aspect of multimodality will be discussed in chapter 2).

1.1 Sensory neglect

Sensory neglect subsumes forms of neglect associated with the selective unawareness of sensory stimuli presented in the contralesional hemispace or hemibody.

As a first factor, sensory neglect may be defined by the *modality* affected in the syndrome complex. Inattention may affect any sensory modality, resulting in a *visual*, *tactile*, *olfactory* or *auditory* neglect, but there are combinations of those modalities as well, e.g. visuo-tactile neglect (Kerkhoff, 2001).

Furthermore, sensory neglect may be defined by the *distribution* of omissions in space (Heilman, Valenstein, & Watson, 2000). Patients with a *personal* neglect fail to attend the left side of their body or the near grasping range (Baas et al., 2011; Committeri et al., 2007), leading to a reduced use of the contralateral extremities as well as disregarding the left side of their body in daily personal hygiene issues. In cases of *spatial* neglect, patients do not respond to sensory stimuli presented in contralesional hemispace, such as described above (see chapter 1). Finally, representational neglect (for review, see Salvato et al., 2014) is defined as a deficit in exploring or describing mental images (Salvato, Sedda, & Bottini, 2014).

1.2 Motor neglect

Motor or *intentional* neglect may manifest itself in the reduction or lack of use of a contralesional extremity during motor activities (for reviews see Punt & Riddoch, 2006; Sampanis & Riddoch, 2006). This immobility is by definition not due to a primary motor lesion or motor deafferentation, though it is often associated with hemiparesis or hemiplegia (Von Giesen et al., 1994; Classen et al., 1997; Punt & Riddoch, 2006; Sampanis & Riddoch, 2013).

In a recent large scale study conducted by Kim and colleagues (Kim et al., 2013), the authors investigated the presence and severity of motor intentional disorders in right vs. left brain damaged patients. Based on the classification of Heilman (Heilman, 2004), the authors focused on hypokinesia or akinesia respectively, which are defined as a deficit of or delay in movement initiation, as well as motor impersistence, defined by an impairment in sustaining actions.

The results indicate a higher incidence rate of motor intentional disorders in right brain damaged patients, whereas, in contrast to previous investigations (Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Bottini, Sterzi, & Vallar, 1992; Mattingley, Bradshaw, & Philips, 1992), no directional or spatial hypokinesia was found in any of the patient groups. Furthermore, both patient groups showed contralesional directional impersistence, although no spatial motor impersistence was observable.

In visual or tactile spatial exploration tasks, hypometria (too small amplitude of leftward eye or manual exploration movements) can be found besides an ipsilesionally shifted exploration pattern (Karnath, Niemeier, & Dichgans, 1998).

1.3 Representational neglect

One of the pioneering studies concerning representational neglect was conducted by (Bisiach & Luzzatti, 1978), which revealed a lack of report in case of objects and scenes on the contralesional side of an imagined visual scene. Interestingly, switching the imaginary position to the opposite side of the imagined place led to reporting things neglected before, now being on the ipsilesional side of the imagined scene. The authors concluded that this result is due to a loss of internal mental representation of space, which leads to a contralesional disregard even of stored representational maps as well as of current contralesional information.

Hence, a concept of *representational neglect* incorporates a failure in recalling details of a contralesional scene or concept affecting *personal* (part their own body, e.g. imagining their right arm) or *spatial* (scenes, familiar places, e.g. their own home) affairs (for review, see Salvato et al., 2014).

2 Multimodal exploration deficits after unilateral brain damage

As mentioned above, neglect as a multimodal phenomenon may affect any sensory (visual, tactile, olfactory and auditory) as well as motor or representational systems. Due to the themes of the present studies, visual, tactile and auditory neglect will be dealt with in more detail below. Additionally, a short outline is given about exploration deficits *beyond lateralized neglect* after unilateral brain damage as well as the crucial brain areas involved in such deficits.

2.1 Crucial brain areas for exploration

The posterior parietal cortex (PPC; Nyffeler et al., 2008; Ellison, Schindler, Pattison, & Milner, 2004) as well as the superior temporal gyrus (STG; Ellison et al., 2004) and the frontal eye fields (Lane, Smith, Schenk, & Ellison, 2012; Anderson et al., 2007) seem to be crucially involved in spatial attention processes as well as exploration of visual scenes (Himmelbach, Erb, & Karnath, 2006). According to recent research, particularly the frontal areas are also associated with working memory functions (Anderson, Mannan, Rees, Sumner, & Kennard, 2010; Heide & Kömpf, 1998).

Based on the research of Treisman and colleagues (Treisman & Gelade, 1980; Treisman & Sato, 1990), two types of visual search processes can be distinguished, namely preattentive, parallel feature search or attentive, serial conjunctive search. Ellison and colleagues (Ellison et al., 2004) applied that feature-integration theory on tasks frequently used in neglect assessment to identify critical brain areas involved in spatial exploration using transcranial magnetic stimulation (TMS) in healthy subjects. They found a clearly disruptive effect of TMS applied on the superior temporal gyrus (STG) in hard visual single feature search tasks, whereas applying TMS on the posterior parietal cortex (PPC) impaired performance in landmark tasks (such as line bisection) and hard visual conjunction tasks (leaned on cancellation tasks) producing deficits similar to those in neglect patients. This is in line with previous research regarding line bisection tasks and cancellation tasks as different syndromes (Rorden, Fruhmann Berger, & Karnath, 2006; Binder, Marshall, Lazar, Benjamin, & Mohr, 1992).

The right frontal eye field (FEF) is supposed to play an important role in saliency managing in explorative tasks (Lane et al., 2012). Depending on the predictability of target location in the sense of priming effects, the right FEF seems to act as a first processing unit recruiting the left FEF as well as the right PPC depending on the necessity of additional attention capacity (Lane et al., 2012; Kalla, Muggleton, Juan, Cowey, & Walsh, 2008).

2.2 Visual and tactile exploration behavior in right brain damaged patients with and without neglect

Several studies in the past have dealt with the specification of various characteristics of exploration behavior in different modalities comparing right brain damaged neglect patients with right- or left-brain damaged as well as healthy control patients. Due to the topics of the present dissertation, visual as well as tactile exploration behavior will be described in greater detail.

Neglect patients show some typical deviations in saccadic eye movements as well as in patterns of eye fixations (Behrmann, Watt, Black, & Barton, 1997; Müri, Cazzoli, Nyffeler, & Pflugshaupt, 2009; Heide & Kömpf, 1998; Karnath et al., 1998; Machner et al., 2012; Mannan et al., 2005). In visual search paradigms, they tend to start right from the objective midline showing more frequent and longer fixations in the ipsilesional, right hemifield (Behrmann et al., 1997; Mannan et al., 2005), with a significantly smaller number of saccades to the contralateral hemifield. In addition, saccades are executed with smaller amplitudes only in the contralateral hemifield (Müri et al., 2009; Karnath et al., 1998). The mean center of exploration (Behrmann et al., 1997; Karnath et al., 1998) as well as head movements and gaze (Karnath et al., 1998) are shifted towards the right of midline. Around this shifted center of exploration, the variability of explorations seems to be decreased, following a bell-shaped form (Karnath et al., 1998; Schindler et al., 2006; Karnath, 1997). Interestingly, bottom-up features of vision, such as high contrast and moving targets, do not ameliorate the general rightward fixation bias in neglect patients whereas in the ipsilesional hemifield, less dynamic contrast is needed to attract patients' attention (Machner et al., 2012).

Modulating factors concerning the extent of omissions in the contralateral hemifield, e.g. in cancellation tasks, seem to be the target arrangement (scattered vs. in organized in rows or columns), the target typology, like verbal vs. nonverbal stimuli (Ronchi, Algeri, Chiapella, Simonetta, & Vallar, 2012), as well as the size of the exploration array (Eglin, Robertson, Knight, & Brugger, 1994). Larger search fields increase a contralesional compared to ipsilesional delay in response times even without changing the total number of stimuli inside the array (Eglin et al., 1994).

Similar findings concerning the ipsilesionally shifted exploration center are reported in tactile search paradigms (Konczak, Himmelbach, Perenin, & Karnath, 1999; Schindler et al., 2006). Although neglect patients typically show decelerated hand movements in tactile search tasks (Konczak et al., 1999), no systematic deficits in goal-directed hand movements (Himmelbach & Karnath, 2003; Karnath, Himmelbach, & Perenin, 2003) or systematic velocity deficits (Konczak et al., 1999) are observable. Based on these investigations, optic ataxia and neglect were considered as two independent neuropsychological phenomena.

Similarly to object- and space-related omissions in neglect patients, the behavioral goal seems to strongly influence the exploration pattern: exploring the whole array leads to omissions in the contralesional hemifield, but if only one segment or part of the whole array is explored, stimuli in the contralesional part of that array may be disregarded (Niemeyer & Karnath, 2002).

Notably, not only brain-damaged patients with neglect are impaired in exploration and search tasks. Recent evidence shows that right brain damaged patients *without* neglect also show deficits compared to healthy controls concerning search or search times. In a recent large scale study by Rabufetti and colleagues (Rabufetti et al., 2012), right- and left-brain damaged patients with and without neglect as well as healthy control subjects performed a visual cancellation task on a touchscreen. The authors found prolonged search times as well as indicators for disorganized search strategies (search path-crossings) in the neglect group, and in an alleviated form also in right brain damaged patients without neglect in the contralesional hemifield, but not in healthy controls. Search times increased with increasing eccentricity. Performance of right brain damaged patients seemed to be placed between those of neglect and healthy control groups. These results indicate that exploration deficits may be associated to right brain damage generally and not exclusively to neglect patients.

According to the literature concerning this question, there is some evidence found for that hypothesis not only for search times, but also for so called perseverative (or revisiting) behavior. Lots of studies found repeated markings of stimuli in cancellation tasks for right brain damaged patients with and without neglect. In fact, these are seen as independent and distinct manifestations of explorative deficits not caused by, but often co-occurring with contralesional neglect by the vast majority of researchers (Ronchi et al., 2012; Na et al., 1999; Rusconi, Maravita, Bottini, & Vallar, 2002; Mannan et al., 2005; Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009; Olk & Harvey, 2006; Pia, Folegatti, Guagliardo, Genero, & Gindri, 2009). In this context, note that perseverative errors are not hypothesized to be part of a spatial working memory deficit, resulting do to a failing memorization of recently visited locations, which can co-occur and exacerbate contralesional neglect (Malhotra et al., 2005; Mannan et al., 2005; Ronchi et al., 2009).

Several modulating factors have been discussed to explain differences in exploration behavior within individual neglect patients in cancellation tasks. Ronchi and colleagues (Ronchi et al., 2012) systematically varied several potentially modulating aspects on omissions and perseverative behavior concerning cancellation tasks and found target disposition (scattered vs. in row) as well as target typology (verbal vs. nonverbal) to be critically modulating outcomes on cancellation tasks. Noteworthy, scattered, nonverbal targets, e.g.in a star cancellation task (Wilson, Cockburn, & Halligan, 1987), seem to affect explorative behavior mostly, leading to higher rates of omissions on the contralesional and more perseverations on the ipsilesional side. Results about target density remain controversial, but it does not seem to affect impairments in neglect (Ronchi et al., 2012; Pia et al., 2009).

Mark and colleagues (Mark, Woods, Ball, Roth, & Mennemeier, 2004) analyzed exploration behavior of patients with mild to moderate neglect with respect to three measurements of spatial organization (marking distance;

number of intersections in the cancellation path and the marking direction (see Mark et al., 2004 for details). None of these measurements was correlated with neglect severity.

In tactile exploration tasks, respectively, neglect can manifest itself other than in typical neglect signs. Haeske-Dewick and colleagues (Haeske-Dewick, Canavan, & Hömberg, 1996) studied near space exploration performance of neglect patients in a visual and a tactile task. While in visual tasks only right brain damaged patients with neglect showed omissions, both right brain damaged groups, with and without neglect signs in other tests, showed a tactile neglect, though it was more frequently observable in the neglect group. Hence, the authors described tactile neglect as a residual symptom which is still observable after a "partial recovery". But note that performance of right brain damaged patients with and without neglect differed in one aspect: neglect patients showed more repetitions in the middle and right areas of the search array though.

A recent investigation by Schindler and collaborators (Schindler et al., 2006) also addressed visual and tactile exploration behavior in right brain damaged patients with and without neglect. The authors used the same exploration task in both modalities allowing a direct comparison between exploration behaviors in the visual vs. the tactile task. Both exploration distribution centers were shifted towards the ipsilesional side, with a statistically significant correlation between the degrees of shift. Exploration centers were similarly shifted with respect to the ipsilesional direction, but they differed in magnitude with stronger impairments in the visual as compared to the tactile modality. Moreover, there was a drop of exploration in the eccentric areas.

2.3 Auditory neglect

Auditory neglect (also known as "spatial deafness") has been reported in numerous studies in the past years (Heilman & Valenstein, 1972; Bellmann, Meuli, & Clarke, 2001; Bellmann Thiran & Clarke, 2003; De Renzi, Gentilini, & Barbieri, 1989; Bisiach, Cornacchia, Sterzi, & Vallar, 1984; Calamaro, Soroker, & Myslobodsky, 1995; Tanaka, Hachisuka, & Ogata, 1999; Zimmer, Lewald, & Karnath, 2003; Pavani, Ladavas, & Driver, 2002; Williams &

Coleman, 2008; Eramudugolla & Mattingley, 2009; Pavani, Husain, Ladavas, & Driver, 2004; Gokhale, Lahoti, & Caplan, 2013). While several studies concerned assessment and treatment of visual neglect, there is much less known about modulating factors in auditory neglect. Both forms of neglect may, but do not always correspond.

Most studies use unilateral sound localization tasks as well as simultaneous dichotic listening tasks to assess auditory impairments in neglect patients (for reviews, see Pavani et al., 2004; Gokhale et al., 2013). Bellmann and colleagues (Bellmann et al., 2001) used a unilateral localization task as well as two simultaneous tasks, a dichotic listening task and an interaural time difference (ITD) diotic task. The latter consisted of 30 pairs of words, which were presented to both ears at the same intensity level but on different sides (right vs. left) to exclude perceptual impairments caused by ear extinction. According to the authors, two types of auditory neglect can be differentiated: i) hemispatial inattention with a deficit in the allocation of auditory spatial attention to the contralesional hemispace following lesions of the basal ganglia as well as ii) a systematic directional bias towards the ipsilesional, i.e. right side with respect to the midsaggital body axis and alloacusis provoked by lesions of the frontotemporoparietal area. Here, alloacusis refers to a subjective shift of contralesional stimuli perceived at the ipsilesional side of the body.

Several cases of auditory extinction are reported in patients with unilateral (most often right-hemispheric) brain lesions (Arboix, Junqué, Vendrell, & Marti-Vilalta, 1996; De Renzi, Gentilini, & Pattacini, 1984; Heilman & Valenstein, 1972; Shisler, Gore, & Baylis, 2004). Despite of a frequent co-occurrence, neglect and extinction are seen as dissociable disorders (for review, see Kerkhoff, 2001).

In line with the well-known dorsal and ventral visual processing system in the human brain (Ungerleider & Haxby, 1994), there is some evidence that the auditory system is also characterized by two distinct pathways processing identification ("what") and localization ("where") tasks (Maeder et al., 2001; Clarke, Bellmann, Meuli, Assal, & Steck, 2000; Clarke & Bellmann Thiran, 2004), which can be impaired and spared separately. The ventral, so called "what"-stream, seems to involve bilaterally middle temporal as well as left inferior frontal areas, whereas the dorsal, "where"-stream is rather associated with parts of the inferior parietal as well as posterior parts of the middle and inferior frontal gyri (Maeder et al., 2001). Based on these results, the two types of neglect mentioned above may be assigned to the dorsal (i.e. directional bias in the contralesional hemispace) and ventral stream processing (i.e. hemispatial inattention; Clarke & Bellmann Thiran, 2004).

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Figure 2.1 illustrates the "what"- and "where" streams in auditory processing (Scott, McGettigan, & Eisner, 2009).

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Figure 2.1: The anatomy of sound perception: The ventral ("what") and dorsal ("where") auditory streams. From the primary auditory cortex (A1), the anterior stream decodes meaning in sounds ("what") and encompasses parts of the auditory association cortex in the STG (dark green) and the inferior frontal gyrus (blue). The posterior pathway has been suggested to be engaged in sensorimotor integration and spatial processing ("how" and "where") and includes parts if the posterior STG, the supramarginal gyrus (green), motor (yellow) and sensory (red) areas and the inferior frontal gyrus (blue)Source: Scott, McGettigan & Eisner (2009), Nature Reviews Neuroscience, 10, Figure 1, page 297.

Furthermore, lots of authors investigated shifts of the subjective perceived vertical with respect to the midsaggital plane of the body in different modalities such as visual (Kerkhoff & Zoelch, 1998; Saj, Honore, Bernati, Coello, & Rousseaux, 2005) or haptic (Kerkhoff, 1999; Funk, Finke, Muller, Preger, & Kerkhoff, 2010). They typically found a clockwise tilt in neglect patients, fitting the concept of neglect as a multimodal spatial orientation deficit (Utz et al., 2011a; Funk et al., 2010). Similarly, neglect patients show an ipsilesional, i.e. rightward shift in the auditory subjective median plane, termed ASMP (Kerkhoff et al., 2006; Kerkhoff et al., 2012; Kerkhoff, Artinger, & Ziegler, 1999; Vallar, Guariglia, Nico, & Bisiach, 1995).

Based on the assumption of neglect as a multimodal disorder, numerous studies evaluated cross-modal therapy approaches to ameliorate multimodal neglect symptoms (detailed information is given below in chapter 3; for a review, see Kerkhoff & Schenk, 2012). Whereas multimodal modulation approaches are already well studied for neck-proprioceptive (Vuilleumier, Valenza, Mayer, Perrig, & Landis, 1999; Schindler & Kerkhoff, 1997; Fujii, Fukatsu, Suzuki, & Yamadori, 1996; Karnath, 1995; Karnath, Christ, & Hartje, 1993) or vestibular stimulation (Saj, Honore, & Rousseaux, 2006; Utz, Keller, Kardinal, & Kerkhoff, 2011b; Oppenländer et al., 2015) in visual and tactile neglect, much less is known about (crossmodal) modulations of auditory neglect. Up to now, bottom-up visual stimulation methods, namely optokinetic stimulation (OKS; Kerkhoff et al., 2012), smooth pursuit eye movement training (Kerkhoff et al., 2013) and prism adaptation (Jacquin-Courtouis et al., 2010) seem to be eligible to ameliorate auditory neglect. Hence, further research is needed to evaluate effects of proprioceptive or vestibular stimulation on auditory neglect.

Kerkhoff et al. (2006) addressed two competing explanation models of the ipsilesional directional shift in auditory neglect mentioned above (Kerkhoff et al., 2006), namely translation (Vallar et al., 1995) vs. clockwise rotation (Karnath, 1997) of the spatial reference frame assessing the auditory subjective median plane in front and back space. In case of patient AJ, they found a contralesional shift in front space accompanied by an ipsilesional shift in back space, suggesting an ipsilesional rotation rather than translation of the spatial reference frame along the midsaggital vertical body axis. Nevertheless, further group research is needed to specify underlying mechanisms in auditory neglect.

3 Multimodal therapeutic accounts

This section provides a short overview about current multimodal therapeutic accounts in neglect treatment. Following some general considerations, sensory treatments, especially proprioceptive as well as vestibular stimulation techniques, are described in more detail because their relation to the goals of the present study.

3.1 General considerations: Top-down vs. bottom-up treatments

Given different explanatory accounts concerning hemispatial neglect (for review, see Kerkhoff, 2001; Karnath, 2006), mainly two different approaches concerning treatment strategies are distinguishable.

First, top-down treatments are functionally based on the initiation of shifting and maintaining attention to the contralesional side, induced by an explicit request of a therapist. In the beginning of such treatments, highly salient cues can be used to facilitate attention shifts to the contralesional hemispace.

The manifold forms of top-down treatments were derived from the different explanatory models of neglect, e.g. attentional training (Sturm, Thimm, Kust, Karbe, & Fink, 2006; Van Vleet & DeGutis, 2013; Schottke, 1997; Kerkhoff, 2001; Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995).

The majority of neglect patients show a lack of conscious awareness about their neglect and the associated deficits, a phenomenon called anosognosia (Stone et al., 1993; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997; Vallar, Bottini, & Sterzi, 2003; Cutting, 1978; Orfei et al., 2007). Anosognosia deteriorates the functional and cognitive outcome after stroke (Vossel, Weiss, Eschenbeck, & Fink, 2013; Dai et al., 2014; Mattioli, Gialanella, Stampatori, & Scarpazza, 2012). Since top-down treatments of spatial neglect need some kind of conscious awareness of the own deficits in order to be effective, anosognosia embodies a general constraint in therapeutic effectiveness concerning top-down treatment methods.

In contrast, bottom-up or sensory stimulation treatments need less conscious awareness about the deficits on hand, forcing up their effectiveness in neglect therapy settings. They are consistent with the view of neglect as a multimodal disorder resulting from a disturbed representation of multimodal spatial coordinates and a common spatial reference frame (Karnath, 1994a; Karnath & Dieterich, 2006; Kerkhoff & Schenk, 2012; Kerkhoff, 2001; Kerkhoff, 2003). This reference frame is assumed to be constituted by different sensory inputs, i.e. visual and auditory inputs, motor efference copies, eye and neck muscle proprioceptive and vestibular information, which are transformed in a multimodal, higher order space representation including the own body in relation to the exterior surrounding field. According to the authors, it is hypothesized to be anatomically represented in the multisensory superior temporal cortex, the temporo-parietal junction as well as the insular cortex (Karnath & Dieterich, 2006; Bottini et al., 2001), whereas damage to these areas is mostly associated with neglect symptoms. As these different sensory inputs are injected into that multisensory spatial frame, changing the “weight” of specific sensory inputs by specific manipulations can be utilized to improve neglect associated deficits by correcting this disturbed reference frame in neglect (Kerkhoff, 2001). Based on this assumption, bottom-up sensory stimulation techniques are capable to ameliorate multimodal deficits even in a crossmodal way (see below).

In the following sections, different techniques of sensory modulation are described in detail (for reviews, see Kerkhoff & Schenk, 2012; Lisa, Jughters & Kerckhofs, 2013). Note that different effects of the same treatments on different patients are observed (Beschin, Cocchini, Allen, & Della Sala, 2012).

3.2 Visual and proprioceptive modulation

3.2.1 Visual modulation: Optokinetic stimulation and Prism adaptation

As far as the visual sensory channel is concerned, there are two major interventions for the amelioration of neglect.

In optokinetic stimulation (OKS), coherent background movement of stimuli (e.g. dots) is used to shift attention to the contralateral hemispace. It is seen as one of the most effective treatments used to ameliorate spatial neglect (Lisa et al., 2013). The therapeutic effect results of an imaginative rotational effect induced by the coherent movement, leading to the perception of body rotation to the ipsilesional side and a consecutive re-orienting to the contralesional, neglected side (Kerkhoff & Schenk, 2012). OKS ameliorates visual (Keller, Lefin-Rank, Losch, & Kerkhoff, 2009; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Thimm et al., 2009; Kerkhoff, Schindler, Keller, & Marquardt, 1999; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Schröder, Wist, & Hömberg, 2008) as well as other neglect associated deficits by means of crossmodal effects (Kerkhoff et al., 2012; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995; Karnath, 1996). Thimm and colleagues (Thimm et al., 2009) investigated behavioral as well as neural effects of OKS on neglect patients by using fMRI. They found increased bilateral activations in the middle frontal gyrus and the precuneus as well as increased unilateral left activation in the cingulate, angular and middle temporal gyrus and visual association cortex, playing, among others, an important role in spatial attention.

Secondly, prism adaptation (PA) is used to ameliorate neglect associated deficits. Prisms lead to a deviation of gaze to the ipsilesional side (Rossetti et al., 1998), unfolding their therapeutic potential by inducing a readaptive after-effect after prism exposure with an attentional shift to the contralesional hemispace (for reviews, see Kerkhoff & Schenk, 2012; Jacquin-Courtois et al., 2013; Striemer & Danckert, 2010; Redding & Wallace, 2006). The differential sensory-motor, functional, cognitive (Rode et al., 2015), postural (Nijboer, Olthoff, Van der Stigchel, & Visser-Meily, 2014) and proprioceptive (Scarpina, Van der Stigchel, Cornelia, Nijboer, & Dijkerman, 2015) effects of PA as well as modulatory factors of PA effectiveness (Goedert, Zhang, & Barrett, 2015; Facchin, Beschin, Toraldo, Cisari, & Daini, 2013; Chen, Goedert, Shah, Foundas, & Barrett, 2014) are still concerns of present research (Jacquin-Courtois et al., 2013; Striemer & Danckert, 2010; Redding & Wallace, 2006; Kerkhoff & Schenk, 2012).

3.2.2 Neck-proprioceptive modulation: Neck muscle vibration, Head-on-Trunk-Modulation and Transcutaneous Electric Nerve Stimulation

Stimulation techniques of the neck muscles, such as neck muscle vibration (NMV) and transcutaneous electrical nerve simulation (TENS), as well as head-on-trunk orientation techniques are used to ameliorate neglect by emending the proprioceptive head-on-trunk input signal.

Several studies in the past years studied ameliorating effects of NMV alone on neglect and associated deficits (Karnath et al., 1993; Karnath, 1995; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 1999; Johannsen, Ackermann, & Karnath, 2003; Schindler & Kerkhoff, 2004) as well as combined with other stimulation techniques (Karnath, 1994b; Saevarsson, Kristjansson, & Halsband, 2010).

Vibration on the left neck induces an apparent lengthening of the neck muscle (Karnath et al., 1993), changing the proprioceptive signal sent by the muscle which is consecutively computed along with other sensory inputs to form the body-centered, egocentric reference frame mentioned above.

Analogous to the preliminary described therapeutic principles, head-on-trunk orientation techniques might also induce a decrease of neglect associated symptoms similarly by modulating proprioceptive input of the neck, realized by a real lengthening of the left neck muscles by turning the head to the right (Karnath et al., 1993; Karnath, 1994b; Karnath, Schenkel, & Fischer, 1991).

Similarly, transcutaneous electric nerve stimulation (TENS) applied on the left trapezium muscle is capable to ameliorate neglect by enhancing proprioceptive sensory information (Vallar, Rusconi, Barozzi, Papagno, & Cesarini, 1995; Pitzalis, Spinelli, Vallar, & Di, 2013; Schröder et al., 2008; Pizzamiglio, Guariglia, Antonucci, & Zoccolotti, 2006) as well as neglect associated deficits (Guariglia, Coriale, Cosentino, & Pizzamiglio, 2000; Guariglia, Lippolis, & Pizzamiglio, 1998; Pérennou et al., 2001; Richard, Rousseaux, & Honoré, 2001; Vallar, Rusconi, & Bernardini, 1996).

3.3 Vestibular modulation

3.3.1 The vestibular system

Caloric and galvanic vestibular stimulation treatments refer to the modulation of vestibular input.

The vestibular system computes information about head rotation and translation, which play an important role for body self-motion, body perception, a sense of gravity, spatial navigation (Lopez & Blanke, 2011), gaze and posture stabilization and reflexive control of gaze, head and body as well as spatial memory (Dieterich & Brandt, 2015; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998; Lopez, Blanke, & Mast, 2012). These functions are realized in collaboration with other sensory systems, integrated in multisensory brain areas (Suzuki et al., 2001) to contribute to a whole body perception and navigation in its environment (for detail, see below). It consists of a peripheral and a central vestibular system, which will be described shortly in the following to provide a common basis for the understanding of neural effects of caloric and galvanic vestibular stimulation (for reviews, see Khan & Chang, 2013; Lopez & Blanke, 2011).

The peripheral vestibular system is located in the inner ear behind the processus mastoideus (Fitzpatrick & Day, 2004). It is composed by the bony labyrinth, consisting of the cochlea and the semicircular canals filled with perilymph fluid, and the membranous labyrinth inside the bony labyrinth, build up by the otolith organs – the utricle and the saccule (Fitzpatrick & Day, 2004; Khan & Chang, 2013) - and three semicircular ducts, filled with endolymphe (Khan & Chang, 2013). The otolith organs contain receptor cells called hair cells, which are depolarized and hyperpolarized by bending caused by movement of the otoliths or the endolymphe surrounding them. Depolarization leads to stimulation of the vestibular nerve while hyperpolarization leads to a reduced firing rate (Khan & Chang, 2013).

The semicircular ducts are oriented to the three planes building a three dimensional vector with each duct being sensitive to its specific plane. This allows the vestibular system to detect head rotational and translational movement in three dimensions of space. Neuronal impulses of the hair cells are accumulated in the vestibular ganglion and its axons partly form the vestibular nerve (Khan & Chang, 2013). The vestibular nerve merges with the cochlear nerve forming the vestibulocochlear nerve, linking the peripheral and the central, thalamocortical vestibular network (Khan & Chang, 2013; Conrad, Baier, & Dieterich, 2014). It consists of four vestibular nuclei in the brainstem as well as nuclei in the thalamus, parts of the cerebellum and the parietal, frontal and occipital cortex as well as subcortical structures like the cingulum and the hippocampus (for reviews, see Lopez & Blanke 2011; Lopez et al., 2012; Conrad et al., 2014). Nuclei in the brainstem are functionally interconnected with motor nuclei of extraocular muscles as well as the spinal cord (Khan & Chang, 2013). They mainly provide reflexive functions such as the vestibulo-ocular reflex (VOR) as well as the vestibulo-spinal reflex (VSR), which play an important role in gaze and posture stability (Dieterich & Brandt, 2015; Khan & Chang, 2013). Furthermore, the thalamus, generally acting as a sensory relay station, is assumed to contribute to multisensory integration processes, whereas the hippocampus seems to be relevant for spatial memory and navigation (Lopez & Blanke, 2011; Khan & Chang, 2013; Dieterich & Brandt, 2015).

On the cortical level, recent functional imaging studies on humans propose the temporo-parietal junction, the intraparietal and central sulcus (Lobel et al., 1998), the medial and posterior insular cortex, the parietal operculum and the retroinsular cortex (Lopez et al., 2012; Lopez & Blanke, 2011) as parts of a cortical vestibular network in humans. In non-human primates, the parieto-insular vestibular cortex (PIVC) is seen as the core region of the vestibular system (Guldin & Grüsser, 1998; Lopez & Blanke, 2011). There are several candidates in the human cortex assumed to be a possible homologue of the PIVC, but the definite location is still discussed controversially (Lopez & Blanke, 2011; Bottini et al., 2001).

3.3.2 Caloric vestibular stimulation

In caloric vestibular stimulation (CVS), cold water is applied in the contralesional or warm water in the ipsilesional ear, leading to stimulation of the horizontal ear canal, increasing the firing rate of the vestibular nerve

(Kerkhoff & Schenk, 2012; Lopez et al., 2012; Utz et al., 2011c). This irritation of the inner ear leads to a slow-phase nystagmus and mostly also to vertigo and nausea making it rather uncomfortable for participants (Bottini et al., 2001; Kerkhoff & Schenk, 2012; Utz et al., 2011c). Nevertheless, CVS has been shown to be able to temporarily ameliorate neglect associated deficits (Karnath, 1994b; Vallar, Bottini, Rusconi, & Sterzi, 1993; Rubens, 1985; Rode, Perenin, Honoré, & Boisson, 1998; Bottini et al., 2001; Rode & Perenin, 1994; Bottini et al., 2005).

In the present study, galvanic vestibular stimulation is applied to modulate vestibular input. Hence, this technique is described in more detail in the following section.

- Aus ***urheberrechtlichen Gründen entfernt*** -

Figure 3.1 illustrates the human vestibular cortices found in imaging studies using vestibular stimulation methods.

- Aus urheberrechtlichen Gründen entfernt -

Figure 3.1: 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. The numbers on the cortex areas refer to the cytoarchitectonic areas defined by Brodmann. Abbreviations: FEF = frontal eye field; VIP = ventral intraparietal area; MIP = medial intraparietal area. Source: Lopez & Blanke (2011), Brain Research Reviews, 67, Figure 3B, page 129.

3.3.3 Galvanic vestibular stimulation

In galvanic vestibular stimulation (GVS), more precisely bilateral bipolar stimulation (Fitzpatrick & Day, 2004), two electrodes (cathode and anode) are applied on the mastoids (for detailed reviews, see Utz, Dimova, Oppenländer &

Kerkhoff, 2010; Fitzpatrick & Day, 2004). Applying weak direct current leads to polarization effects on the otoliths as well as the semicircular canals (Stephan et al., 2005) inducing an increased firing rate of vestibular afferents ipsilaterally to the cathode and a decreased firing rate ipsilaterally to the anode by hyperpolarization of the afferents. These effects lead to stimulation of the vestibular nerve, thus activating the whole thalamocortical pathway up to cortical vestibular areas (Utz et al., 2010; Fitzpatrick & Day, 2004). Figure 3.2 illustrates the mechanism of GVS schematically.

- Aus Datenschutzgründen entfernt -

Figure 3.2: Schematic illustration of the mechanism of GVS. Stimulation is transmitted in the vestibular nerve and any further relay stations on the way to the parieto-insular vestibular cortex. Source: Utz et al. (2010), Neuropsychologia, 48, Figure 3, page 2794.

Notably, left-anodal/right-cathodal GVS leads to unilateral activation of the right-hemispheric vestibular system, while left-cathodal/right-anodal GVS leads to a bilateral activation of both vestibular cortices (Fink et al., 2003).

Fink and colleagues (Fink et al., 2003) investigated the effects of a galvanically induced interference with the egocentric spatial reference frame in healthy subjects who performed simultaneously to GVS-stimulation an allocentric spatial task. They found bilateral activation increases (as measured by fMRI) in the posterior part of the insula, the superior temporal gyrus and the inferior parietal cortex, in accordance with previous findings (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bottini et al., 1994; Bottini et al., 2001). Interestingly, these areas are affected in the majority of neglect patients, implicating a great therapeutic potential on GVS for neglect rehabilitation in the future. By now, there is a lot of evidence validating that assumption with respect to neglect and associated deficits (Oppenländer et al., 2014; Volkening et al., 2014; Utz et al., 2011b; Kerkhoff et al., 2011; Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010; Schmidt, Keller, Artinger, Stumpf, & Kerkhoff, 2013a).
Beside that therapeutic power, recent safety investigations do not suggest any strong side effects or safety restrictions during the use of GVS (Iyer et al., 2005; Utz et al., 2011c), making that technique even more attractive.

4 Experiment 1 –Multimodal neglect and its modulation capability using Galvanic Vestibular Stimulation

Several studies have addressed the modulation of deficits in exploration behavior due to right brain damage. As described in section 2, right brain damaged patients with and without neglect seem to show typical deficits.
Most studies address neglect associated deficits in the visual modality. Hence, less is known about tactile neglect, which in fact is harder to assess due to a lack of standardized diagnostic tools. The first issue of the present dissertation was therefore to address was the following:

(i) Are standardized visual neglect screening tests suitable to detect neglect associated deficits in visual and tactile exploration tasks?

As a second aspect of multimodality, exploration behavior may vary between and within different patients with neglect, as a result of the modality tested. This may lead to associations or dissociations in task performance across different modalities. Hence, the second question is the following:

ii) Does task modality influence the pattern of exploration behavior in subjects with neglect? And how do neglect patients differ from healthy and right brain damaged controls?

With respect to modality specific exploration patterns, we tried to replicate the findings of Schindler et al. (Schindler et al., 2006) by using the same exploration task for both the visual and tactile modality for a direct comparison.

Several studies investigated differences in explorative performance comparing neglect patients and right brain damaged control subjects. Some found deficits in right brain damaged controls, which quantitatively lay between the performance of neglect patients and healthy controls. This leads to the third issue of the following experiment:

(iii) Do right brain damaged controls show omissions and perseverations in spatial exploration tasks? How do they perform in comparison to neglect patients and healthy controls?

According to Fink et al. (2003), GVS may represent a very promising technique for the treatment of neglect. We used GVS stimulation in different conditions in the present dissertation in order to compare baseline and stimulation performance of the neglect patients. This leads to the fourth issue investigated in the present study:

(iv) Does GVS have a polarity-specific influence on search behavior in the visual and / or tactile modalities?

4.1 Methods

4.1.1 Subjects

Eight right-handed patients with unilateral right hemispheric damage and with neglect (termed "N+" in the following; mean age 68,4 years; SD 11,27), eight right-handed, unilaterally right brain damaged patients without neglect (termed "RBD" in the following; mean age 59,8 years; SD 8,73) as well as eight healthy right-handed control subjects (called "Controls" in the following; mean age 64 years, SD 9,53) were tested.

Age was matched between all subjects (Kruskal-Wallis-Test, Chi square=2,717, df=2, p>0.05). All participants were informed about the purpose of the study and gave their informed written consent for their participation. Detailed information about brain damaged participants with (see Table 4.1) and without neglect (see Table 4.2) is given below.

Additionally, time since lesion was matched and did not differ significantly between the patient groups (Mann-Whitney-Test, Z= -0,378, p>0.05).

Patient groups were partitioned by a neglect screening (for detail, see Chapter 4.1.2) into those showing left neglect versus those who did not show left neglect according to cutoff criteria. Binocular visual fields were measured in all patients with a Tübingen or Goldmann perimeter to diagnose hemianopia or other types of postchiasmatic visual field disorders. In addition, all participants were interviewed with a handedness questionnaire and their visual acuity was measured with a letter acuity chart (Oculus Nahleseprobe) in the viewing distance of 0.4 m (minimum visual acuity was 0.50 = 50% in all subjects).

Exclusion criteria were pre-existing neurological diseases, bilateral and left-sided lesions as well as psychiatric disorders. Furthermore, contraindications of galvanic vestibular stimulation were considered, such as parts of metal in the body, epileptic seizures in the anamnesis, pregnancy or a heart pacemaker, which suspended participation in the present investigation.

Table 4.1: Demographic and clinical data of right brain damaged patients with neglect (N+) of experiment 1. Abbreviations: TSL: Time since lesion (months); Field sparing: Visual field assessed with a perimeter; Bisect: Line bisection of 20 horizontal lines in different positions on a landscaped page (+ / -: rightward / leftward deviation in mm of the subjective compared to the objective midline); Letter canc.: letter cancellation task (+ / -: more / less than 2 omissions on one half of the page); number canc.: number cancellation; star canc.: star cancellation; Copy: Copying of three drawings (+ / -: omissions or size distortions in the subject's drawing); neglect dyslexia: Results of a standardized neglect dyslexia sensitive reading text; Mobility: 0= normal, 1=Hemiparesis, 2=Hemiplegia; MCI: middle cerebral artery infarction; CVE: cerebrovascular event; temp, par, front, occ: temporal, parietal, frontal, occipital; CI: capsula interna; Thal: Thalamus; HH: homonymous hemianopia (see text for details).

Code	Age Sex	Aetiology	Visus	Lesion Location	TSL	Field sparing	Bisect (mm)	Letter canc. L/R	Number canc. L/R	Star canc. L/R	Copy L/R	Neglect dyslexia	Mobility
N+1	66,m	MCI	1	right temp	1,5	Normal	32,2 (+)	-/+	-/+	-/+	-/+	yes	1
N+2	67,m	MCI	1	right temp	1	Normal	11,69 (+)	-/+	-/+	+/+	+/+	no	1
N+3	81,m	MCI	0,8	right temp	2	HH left	55 (+)	-/-	-/-	-/-	-/+	yes	2
N+4	83,m	MCI	0,8	right temp	2	Normal	10,6 (+)	+/+	+/+	+/+	+/+	no	1
N+5	55,m	CVE	1,25	right temp-par	8	HH left	4,5(+)	+/-	-/-	-/+	-/+	no	1
N+6	51,w	CVE	0,63	right occ, CI, Thal.	152	HH left	5,3(-)	-/-	+/-	-/-	+/+	no	0
N+7	69,w	semiMCI	1	right front-temp	1,5	Normal	2,8 (-)	-/+	+/+	+/-	+/+	no	0
N+8	74,m	MCI	0,5	right temp-par	22	HH left	16,2(+)	+/+	+/-	+/+	+/-	no	0
Mean	**68,4**	**MCI**	**0,87**		**23,6**		**15,26 (+)**						

Table 4.2: Demographic and clinical data of right brain damaged patients without neglect (RBD) of experiment 1. Abbreviations: TSL: Time since lesion (months); Field sparing: Visual field, assessed with a perimeter; Bisect: Line bisection of 20 horizontal lines in different positions on a landscaped page Letter canc.: letter cancellation task; number canc.: number cancellation; star canc.: star cancellation; Copy: Copying of three drawings; neglect dyslexia: Results of a standardized neglect dyslexia sensitive reading text; Mobility: 0= normal, 1=Hemiparesis, 2=Hemiplegia: ; ICB: intracerebral bleeding; semiMCI: partial middle cerebral artery infarction; ISC: ischemic brain damage; MCI: middle cerebral artery infarction; CVE: cerebrovascular event; temp, par, front, occ: temporal, parietal, frontal, occipital; BG: basal ganglia; CE: capsula externa; HH: homonymous hemianopia (see text for details).

Code	Sex Age	Aetiology	Visus	Lesion Location	TSL (months)	Field sparing	Bisect (mm)	Letter canc. L/R	Number canc. L/R	Star canc. L/R	Copy L/R	Neglect dyslexia	Mobility
RBD-1	73,w	ICB	1	right BG	2	Normal	2,92 (-)	+/+	-/+	-/-	+/+	no	0
RBD-2	53,m	CVE	0,63	right temp-par	27	HH left	3,1 (+)	+/+	-/-	+/+	+/+	no	1
RBD-3	62,m	MCI	1	right temp-occ	1	HH left	3,07 (+)	+/+	+/+	+/+	+/+	no	1
RBD-4	51,w	CVE	0,8	right temp-pa	17	HH left	2,0(-)	+/+	-/-	-/+	+/+	no	1
RBD-5	55,m	ISC	1	right BG	1	Normal	1,94 (-)	+/+	+/+	+/+	+/+	no	0
RBD-6	50,m	ISC	1	right CE	1	Normal	3,7 (-)	+/+	+/+	+/+	+/+	no	1
RBD-7	65,w	CVE	0,63	right temp-par	17	Normal	1,0(+)	+/+	-/-	-/-	+/+	no	1
RBD-8	69,m	ICB	0,63	right BG	40	HH left	1,7(-)	-/-	-/-	-/-	+/+	no	2
Mean	**59,8**		**0,84**		**13,3**		**0,64 (-)**						

4.1.2 Neglect tests

Both patient samples underwent the following six neglect screening tests (see below), namely line bisection, three cancellation tests, a copy drawing test and a reading test. Patients were attributed to the N+ group if a) they showed abnormal search patterns in at least one of the three cancellation tests or b) showed a rightward deviation of the subjective line midpoint of at least 5 mm.

4.1.2.1 Line Bisection (Schenkenberg, Bradford, & Ajax, 1980)

Subjects bisected 20 horizontal lines presented on a landscaped page, differing in length and position (left, middle, right).

Performance patterns were computed with respect to the line’s position on the page. A rightward shift of the subjectively perceived line midpoint is quantitatively assessable. A deviation of the subjectively perceived compared to the objective line midpoint > 5 mm was set as an indicator of contralesional neglect.

4.1.2.2 Cancellation tasks

Three types of cancellation tasks were used, thereby varying the different modulatory aspects in search as mentioned above (see chapter 2.2).

In the Letter Cancellation Task (Wilson, Cockburn, & Halligan, 1987), letters were presented in rows across a landscaped page. Targets were E’s and R’s within rows of distracting letters.

In the Number Cancellation Task (Wilson et al., 1987), a “cloud” of 200 digits, all ranging from 1 to 9, was presented on a landscaped page. Patients were asked to cancel any digit “5” on the page. Each hemispace of the test consisted of 10 target digits and 90 distractors.

In the Star Cancellation Task (Wilson et al., 1987), black stars as well as words written in capital letters were scattered across the landscaped page. Patients had to highlight any small star.

For any cancellation task, cut-off value for pathological performance was set at more than two contralateral omissions.

4.1.2.3 Reading Text

The standardized paragraph reading text (Wilson et al., 1987) was applied to indicate neglect dyslexia. The text was subdivided into three columns (left, middle, right), each consisting of two passages. The columns contained 142 neglect sensitive words (47 words in the left, 47 in the middle and 48 in the right column). Misreading or omission of more than two words per column indicated neglect dyslexia.

4.1.2.4 Copy Drawing Task

In the Copy Drawing Task (Wilson et al., 1987), three drawings are presented on an edgewise page separated by grid lines. Patients were asked to copy a star, a bisected rhombus and a flower presented on the left half of the page drawing it on the right side. This subtest is regarded as a sensitive measure of object-based neglect. Drawing performance was evaluated by the use of a standardized criterion catalogue awarding each picture with a score of three points at maximum.

4.1.3 Exploration table

A large exploration table was built based on the study from Schindler and colleagues (Schindler et al., 2006), covering 240° of the patients surrounding peripersonal area (see Figure 4.1).

A total sum of 96 stimuli in three different shapes (triangles, squares, circles) was placed randomly all over the board. Consequently, each half of the table contained a set of 48 stimuli (16 triangles, 16 squares, 16 circles). Stimuli were matched in size, about 4cm x 4cm each. In order to allow those stimuli to serve as targets in both the visual and tactile tasks, a capital letter or a digit was placed on the top of each stimulus as a distinctive mark. Labels were randomly applied on the stimuli across the table.

Participants' ability to distinguish the three shapes was tested prior to the experimental tasks. Each kind was handed out to the blindfolded participants, who were asked to identify the shape by using only the right hand. All participants were able to differentiate haptically between the presented shapes.

In the visual condition, each of the 96 stimuli had to be named by terms of shape and attached label (e.g. “Square D”) using only the visual modality.
In the tactile condition, blindfolded subjects were asked to name each stimulus’ shape by only using the ipsilesional, i.e. right hand.
In both conditions, subjects were requested to perform as quickly and efficiently as possible. Time required to explore the whole board was recorded with a stopwatch for each trial from the investigator’s starting sign until participants indicated their exploration to be completed.
Evaluation of performance was realized by the help of audio and video recordings. Exploration patterns were assigned on schemata depicting the spatial arrangement of stimuli on the exploration table (see Figure 4.1). Omissions and repetitions were scored separately for each of the eight sectors.

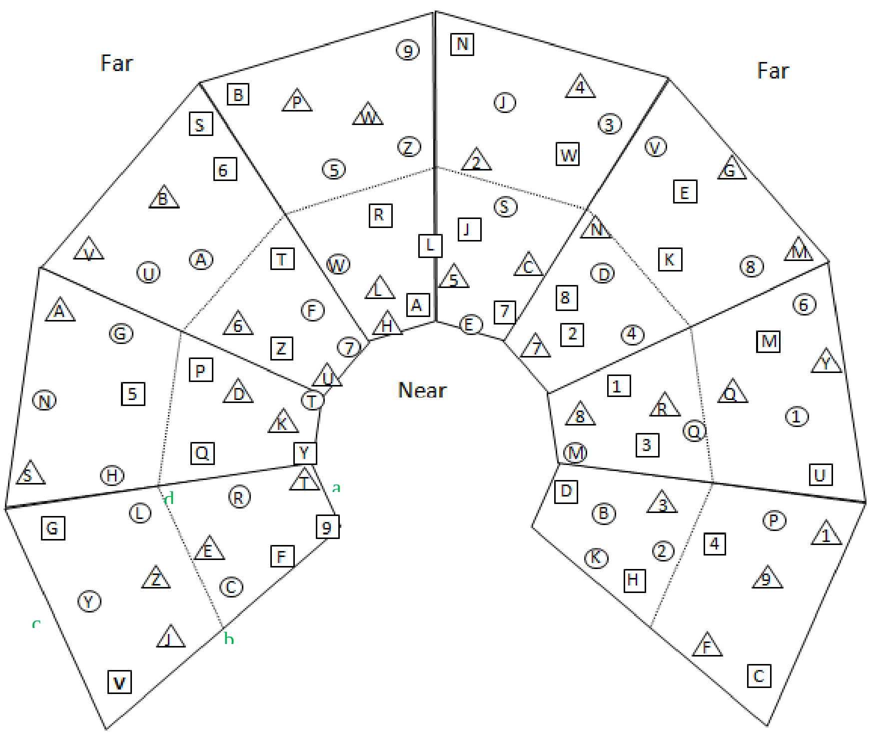

Figure 4.1: Exploration table - schematic view. 12 stimuli are set in each of the 8 sectors (6 near space, 6 far space), resulting in a sum of 96 stimuli on the exploration table. The size of each of the eight test segments was 22,5 x 80 x 60 x 84 (a x b x c x d; cm).

4.1.4 Galvanic Vestibular Stimulation

All participants were stimulated with bilateral bipolar GVS. A 9-voltage battery-driven constant direct current stimulator was used in three stimulation conditions. Electrodes were covered in 6x4cm sized saline-soaked sponges preventing subjects' skin from any possible injury done induced by the electric current. The subjects were unaware of the stimulus conditions during the test sessions and never saw the stimulation device.

In the left-cathodal condition (GVS-CL), the cathode was placed over the left mastoid while the anode was located at the right mastoid.

In analogy, in the right-cathodal condition (GVS-CR), the cathode and anode positions were reversed.

In a third placebo / sham condition (GVS-Sham), electrodes were fastened on the mastoids with the cathode on the left side, but current flow was terminated after 10 seconds. This modus operandi was applied because it is known from studies of transcranial direct current stimulation (tDCS) that a quick habituation of the skin sensations occurs which makes subjects unable to distinguish between current verum stimulation and the placebo/sham condition described here. This allows to manipulate the stimulation conditions of GVS including placebo stimulation without the subject being aware about the real stimulation conditions (Iyer et al., 2005), because they never feel the typical tingling sensation of the current under the anode. The latter was achieved by setting the stimulation intensity always below the individual threshold (hence "subliminal"). This threshold was individually determined in each subject at the beginning of each stimulation session (Utz et al., 2010). Electric current was faded in gradually in steps of 0,1 mA per second until subjects reported a slight prickling on their skin below the electrodes. Then, current intensity was decreased gradually until this skin sensation was not noticeable anymore. This threshold determination was undertaken twice in order to re-evaluate the individual subliminal threshold. Finally, participants were never allowed to see the GVS stimulation device or any setting on.

For each search condition, two visual (A) and two tactile (B) trials were conducted.

Normal subjects and patient groups were split into two subgroups which performed the search tasks in a different sequence. Group A (odd subject numbers) always passed through an “AB-BA” sequence intercepted by a short break after two trials, whereas Group B (even subject numbers) always followed a “BA-AB” order starting with the tactile task.

4.1.5 Procedure

4.1.5.1 Control subjects

All control subjects took part in three sessions.

In the first session, participants were assigned to one of two subgroups (A vs. B) defining the task sequence (visual-tactile vs. tactile-visual) applied in any condition.

Figure 4.2 illustrates the study design for healthy controls. Prior to being exposed to GVS, the first session, Baseline tasks as well as sham stimulation (GVS-Sham) were passed to avoid any influence on task performance by earlier GVS stimulation sessions.

In the second and third sessions, the cathode-left (GVS-CL) and cathode-right (GVS-CR) stimulations were performed in a pseudorandom sequence. In half of the subjects the sequence was Baseline – GVS-Sham – GVS-CL – GVS-CR; in the other half the sequence was Baseline – GVS-Sham – GVS-CR – GVS-CL. After each stimulation session, a potential after-effect was measured after 20 minutes.

Each session consisted of two visual and two tactile baseline trials, two visual and two tactile stimulation trials as well as two visual and two tactile after-effect trials. There was a 20-minute break between stimulation and aftereffect blocks. Between different experimental conditions (GVS-Sham, GVS-CL, GVS-CR), a period of at least three days was implemented in order to control for carry-over effects. For the same reason, prior to each stimulation session two visual and two tactile baseline trials without GVS-stimulation (Base-Pre-CL/-CR) were performed.

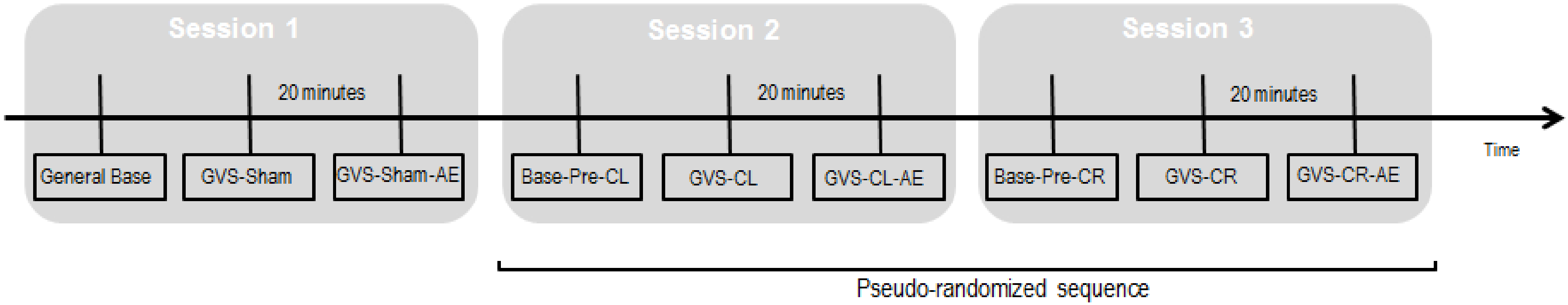

Figure 4.2: Study design of experiment 1 for healthy controls. Abbreviations: GVS-CL: left cathodal / right anodal GVS; GVS-CR: right cathodal / left anodal GVS; General Base: general baseline; Base-Pre-CL: Baseline trials assessed prior to GVS-CL-stimulation. Base-Pre-CR: Baseline trials assessed prior to GVS-CR-condition; AE: aftereffect.

4.1.5.2 Brain damaged subjects

Figure 4.3 illustrates the study design for patient subgroups (RBD, N+). All brain-damaged subjects participated in four sessions.

In the first session, the neglect screening tests described above were given to distinguish between the patient groups (N+ and RBD). After that, a baseline performance in the different versions of the search table (visual or tactile) was recorded.

From the second to the fourth session, baseline trials (two for each modality) were administered, followed by stimulation sessions. Verum stimulation sessions (GVS-CL und GVS-CR) and the placebo session (GVS-Sham) were presented in a randomized order to avoid any sequence effects. According to Gandiga and colleagues (Gandiga, Hummel, & Cohen, 2006), the patients are unable to distinguish between the placebo and the stimulation sessions.

Importantly, the internal sequence of the experimental sessions was identical in control subjects, N+ and RBD subjects.

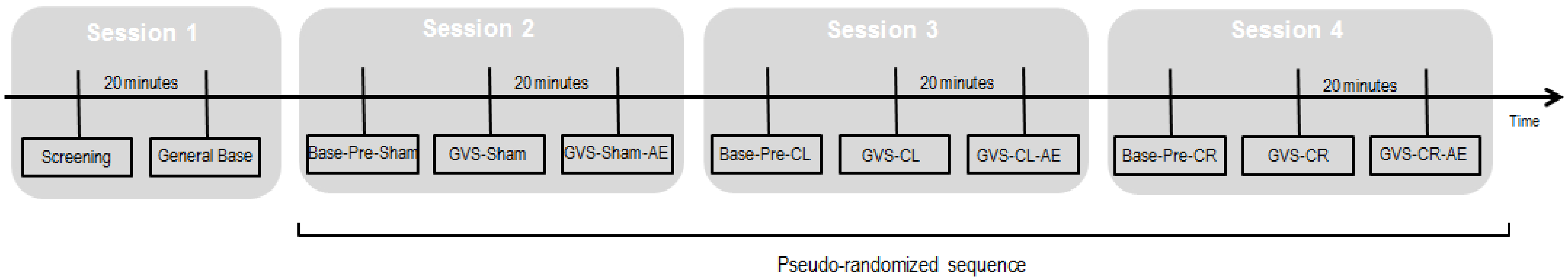

Figure 4.3: Study design of experiment 1 for patient subgroups (N+, RBD). In the first session, a visual neglect screening was assessed prior to a general baseline (see text for details). Abbreviations: GVS-Sham: Sham / placebo condition; GVS-CL: left cathodal / right anodal GVS; GVS-CR: right cathodal / left anodal GVS; General Base: general baseline; Base-Pre-CL: Baseline trials assessed prior to GVS-CL-stimulation. Base-Pre-CR: Baseline trials assessed prior to GVS-CR-condition; AE: aftereffect.

4.1.6 Statistical analyses

All statistical analyses were calculated with SPSS Statistics, Version 22.
Average scores of omissions and perseverations in each hemifield of the exploration table were used to compare performances within and between groups.
Due to the fact that assumptions for ANOVAs (normal distribution) were not met (Kolmogorov-Smirnov-Tests, $p \leq .20$), data was analyzed non-parametrically.
Subject groups (Controls, N+, RBD) were compared regarding age (Kruskal-Wallis-Test) and patient groups (N+, RBD) regarding time since lesion (Mann-Whitney-Test). No significant differences were found concerning those two parameters (see section 4.1.1).

Baseline trials for each condition (general Baseline condition, GVS-CL, GVS-CR, GVS-Sham) were compared separately for the three subject groups (Controls, N+, RBD) using Friedman-Tests for visual and tactile tasks, omissions and perseverations as well as left and right hemispace. Since no differences found between the baselines in any group, further calculations were conducted with the first, general baseline only, (averaged two visual trials as visual baseline, averaged two tactile baselines for tactile trials; see Table 4.3).
Wilcoxon Tests were carried out for each subgroup separately to compare effect of task modality (see Table 4.5) as well as lateralization (see Table 4.6) in baseline conditions with respect to exploration performance parameters (omissions vs. perseverations) and hemispace (left vs. right).
Furthermore, Friedman-Tests were conducted between all three subject groups (Controls, N+, RBD) comparing the effect of conditions (general Baseline vs. GVS-CL vs. GVS-CR vs. GVS-Sham) separately for modality (visual vs. tactile) and exploration performance (omissions vs. perseverations). Significant differences were analyzed in paired comparisons (N+ - RBD, N+ - Controls, RBD – Controls) using Mann-Whitney- Tests (two-tailed, $\alpha = .05$).
The effect as well as aftereffects of GVS were analyzed within patient groups using Friedman-Tests (df=3, two-tailed, $\alpha = .05$) to reveal any GVS-associated

improvements or impairments. Significant results were specified using Wilcoxon-Tests (n=8, $\alpha = .05$).

4.2 Results

4.2.1 Baseline Homogeneity

At the beginning of each session, two baseline trials in each modality were conducted in order to avoid any bias induced by repeated task execution or after effect of previous stimulation.

Baseline trials were compared within each group (N+, RBD, normal controls) using Friedman-Tests, calculated for omissions and perseverations separately concerning modality (visual vs. tactile) and hemispace (left vs. right). No significant results were found in any group (df=3, $p > .05$) (see Table 4.3 for detailed information). Hence, further calculations were computed using only the general, averaged baseline described above.

Table 4.3: Results (Chi^2, p) of the Friedman-Tests comparing the baseline conditions (see text for details).

	Modality	**Hemi-space**	**Controls (n=8)**		**N+ (n=8)**		**RBD (n=8)**	
			Chi^2	*p*	*Chi^2*	*p*	*Chi^2*	*p*
Perseverations	*Visual*	Left	4,962	.175	3,0	.392	2,583	.460
		Right	4,6	.204	4,167	.244	4,167	.244
	Tactile	Left	3,111	.375	5,4	.145	2,833	.418
		Right	0,444	.931	3,167	.367	3,917	.217
Omissions	*Visual*	Left	1,286	.733	2,294	.514	1,8	.615
		Right	2,294	.514	1,5	.682	6,6	.086
	Tactile	Left	3,115	.374	5,5	.139	5,5	.139
		Right	0,444	.931	0,5	.919	0,5	.919

4.2.2 Task comparison regarding modality

The effect of modality was analyzed for each subgroup separately (Controls, N+, RBD) with respect to exploration performance (omissions vs. perseverations) and hemispace (left vs. right).

Mean perseverations and omissions are shown in Table 4.4.

Table 4.4: Mean numbers (and standard deviations) for omissions and perseverations in the baseline conditions, separately for the three subject groups (Controls, N+, RBD), hemispace (left, right) and modality (visual, tactile).

	Modality	**Hemi-space**	**Controls (n=8)**		**N+ (n=8)**		**RBD (n=8)**	
			Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Perseverations	*Visual*	Left	2,56	1,94	5,94	6,48	8,31	8,19
		Right	1,13	0,83	7,63	7,30	8,13	5
	Tactile	Left	9,75	9,02	6	6,94	8,5	4,52
		Right	8,44	8,17	9,56	7,31	7,19	5,98
Omissions	*Visual*	Left	0,81	0,88	15,44	14,23	3,75	4,61
		Right	1,81	1,51	12,5	11,89	4,31	3,96
	Tactile	Left	8,56	5,05	24,5	14,01	17,13	9,75
		Right	10,88	5,13	17,5	6,34	17,13	5,79

Table 4.5 shows exact results of the Wilcoxon Tests for healthy controls and patient subgroups.

For healthy controls, performance in the tactile task was consistently worse than performance in the visual task for omissions as well as for perseverations ($p < .05$, n=8, $\alpha = .05$ two-tailed). Interestingly, both patient groups only showed significant differences in explorative performance as far as omissions are concerned. Repeated search (perseverations) was not significantly affected by task modality (n=8, two-tailed, $p > .05$).

*Table 4.5: Results (Z, p) of the Wilcoxon Tests for healthy controls and patient subgroups (N+, RBD) comparing the task modality in the baseline and in different GVS-conditions (see text for details). *: significant difference (p<.05)*

		General Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
Healthy Controls		*Z*	*P*	*Z*	*p*	*Z*	*p*	*Z*	*p*
Perseverations	*Left*	-2,103	**.035***	-2,380	**.017***	-1,960	**.05***	-2,366	**.018***
	Right	-2,524	**.012***	-2,521	**.012***	-2,111	**.035***	-2,103	**.035***
Omissions	*Left*	-2,521	**.012***	-2,524	**.012***	-2,521	**.012***	-2,521	**.012***
	Right	.2,524	**.012***	-2,521	**.012***	-2,524	**.012***	-2,521	**.012***
N+									
Perseverations	*Left*	-0,512	.609	-0,911	.362	-0,07	.944	+0,631	.528
	Right	-0,771	.441	-1,183	.237	+0,281	.778	0	1,0
Omissions	*Left*	-2,197	**.028***	-2,035	**.042***	-2,521	**.012***	-2,524	**.012***
	Right	-1,12	.263	-1,122	.262	-2,521	**.012***	-2,521	**.012***
RBD									
Perseverations	*Left*	-0,07	.944	+0,845	.398	+0,14	.889	+0,631	.528
	Right	+0,211	.833	+0,844	.398	+0,281	.778	+0,338	.735
Omissions	*Left*	-2,521	**.012***	-2,521	**.012***	-2,521	**.012***	-2,524	**.012***
	Right	-2,521	**.012***	-2,380	**.012***	-2,521	**.012***	2,521	**.012***

4.2.3 Lateralization of omissions and perseverations in patient subgroups concerning baseline performance

Comparisons within patient groups (N+, RBD) using Wilcoxon-Tests for baselines concerning left and right hemispace showed higher mean perseveration rates for neglect patients in right hemispace as well as higher omission rates in left hemispace, though differences did not reach a significant level (see Table 4.6). Notably, for RBD-group, no systematic lateralization tendencies are indicated by data.

Table 4.6: Mean numbers of perseverations and omissions as well as results (Z, p) of the Wilcoxon Tests for patient subgroups (N+, RBD) comparing hemispace (left vs. right) in visual and tactile modality (see text for details).

		Mean (SD)		**Wilcoxon Test**	
N+		*Left*	*Right*	*Z*	*p*
Perseverations	*Tactile*	6 (6,94)	9,56 (7,31)	1,26	.208
	Visual	5,94 (6,48)	7,63 (7,3)	0,563	.0574
Omissions	*Tactile*	24,5 (14,1)	17,5 (6,34)	-1,26	.208
	Visual	15,47 (14,29)	12,5 (11,89)	-0,84	.40
RBD		*Left*	*Right*	*Z*	*P*
Perseverations	*Tactile*	8,5 (4,52)	7,19 (5,98)	-0,28	.779
	Visual	8,31 (8,19)	8,13 (5)	-0,281	.779
Omissions	*Tactile*	17,13 (9,75)	17,13 (5,79)	-0,169	.866
	Visual	3,75 (4,61)	4,31 (3,96)	0,762	.446

4.2.4 Group differences in GVS stimulation sessions

Kruskal-Wallis-Tests (df=2, $\alpha < .05$) were calculated separately for each modality (visual vs. tactile), hemispace (left vs. right) and performance criterion (perseverations vs. omissions).

4.2.4.1 *Perseverations*

4.2.4.1.1 *Tactile task*

Mean numbers of perseverations in the tactile task for left (Figure 4.4) and right (Figure 4.5) are illustrated graphically below.

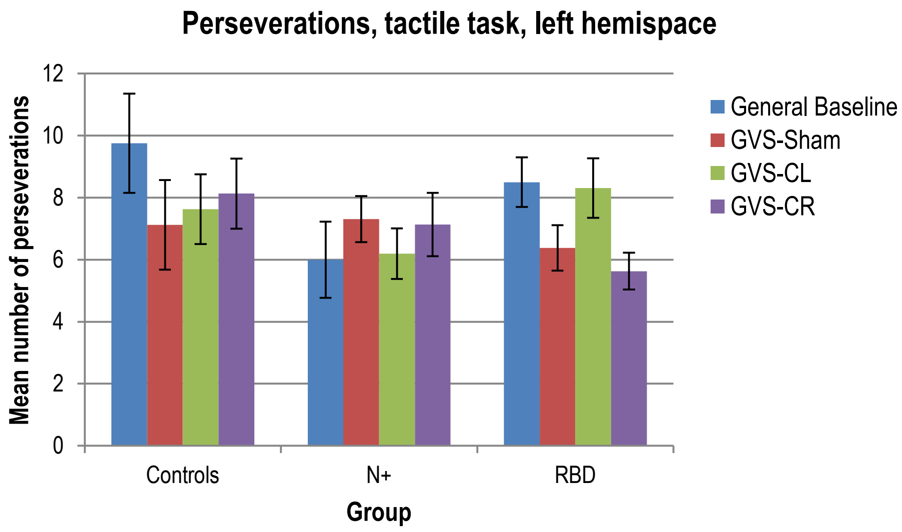

Figure 4.4: Mean numbers (and standard errors of the means) of perseverations in the left hemispace in the tactile task for the three subject group (Controls, N+, RBD; see text for details).

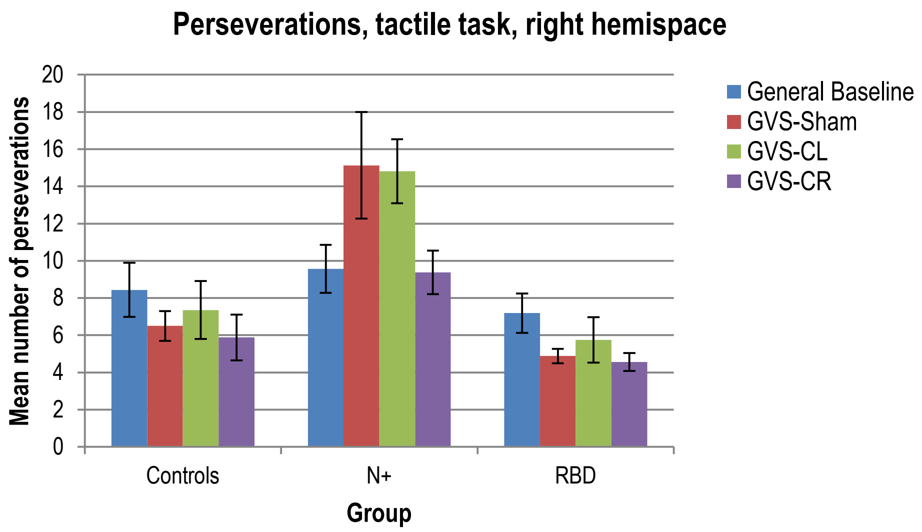

Figure 4.5: Mean numbers (and standard errors of the means) of perseverations in the right hemispace in the tactile task for the three subject groups (Controls, N+, RBD; see text for details).

While all groups performed on a similar level in left hemispace concerning perseverations, significant group differences were found in right hemispace only for the GVS-CL condition (Kruskal-Wallis, Chi^2=6,077, df=2, p=.048; see Table 4.7 for detailed information). Graphical analysis of mean numbers of perseverations in left hemispace revealed that healthy controls performed on patient's performance level or even worse, emphasizing the challenging nature of the tactile task.

*Table 4.7: Results (Chi^2, p) of the Kruskal-Wallis-Tests comparing the mean numbers of perseverations in the tactile task between the three subject groups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	Chi^2	*p*	*Chi^2*	*p*	*Chi^2*	*p*	*Chi^2*	*P*
left	2,02	.364	0,186	.911	0,393	.822	0,588	.745
right	0,406	.816	4,824	.090	6,077	**.048***	5,368	.068

Paired comparisons (U-Tests, see Table 4.8) for right hemispace showed significant differences between N+ and RBD for GVS-Sham (U=13, p=.05), GVS-CL (U=12, p=.038) and GVS-CR (U=13,5, p=05) as well as between N+ and Controls for both verum stimulation conditions (GVS-CL-condition: U=12, p=.038; GVS-CR condition: U=13, p = .05).

*Table 4.8: Results (U, p) of paired comparisons comparing the mean number of perseverations in the right hemispace for the tactile task between subject groups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*P*
N+ - RBD	25	.505	13	**.05***	12	**.038***	13,5	**.05***
N+ - Controls	30	.878	16	.105	12	**.038***	13	**.05***
RBD – Controls	30	.878	27	.645	28,5	.721	29	.798

4.2.4.1.2 Visual task

Mean numbers of perseverations in the visual tasks for left (Figure 4.6) and right (Figure 4.7) hemispace are shown below.

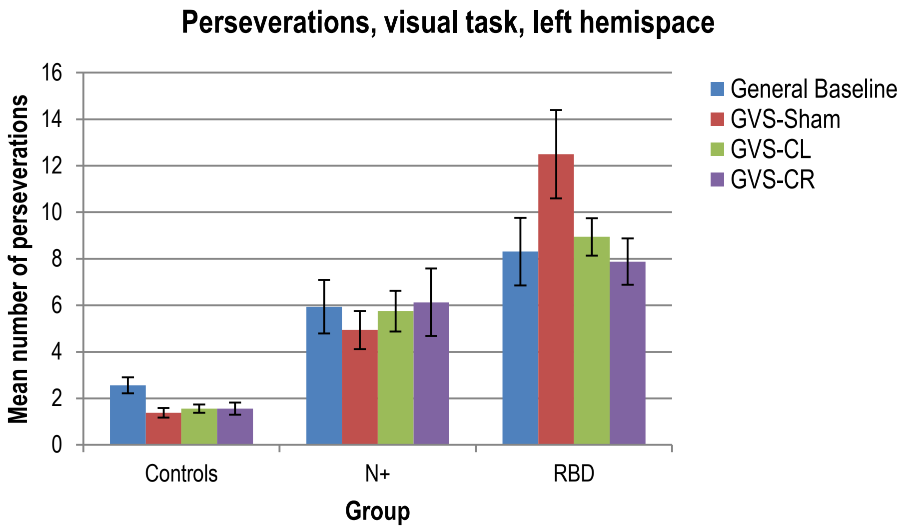

Figure 4.6: Mean numbers (and standard errors of the means) of perseverations in the left hemispace in the visual task for the three subgroups (Controls, N+, RBD; see text for details).

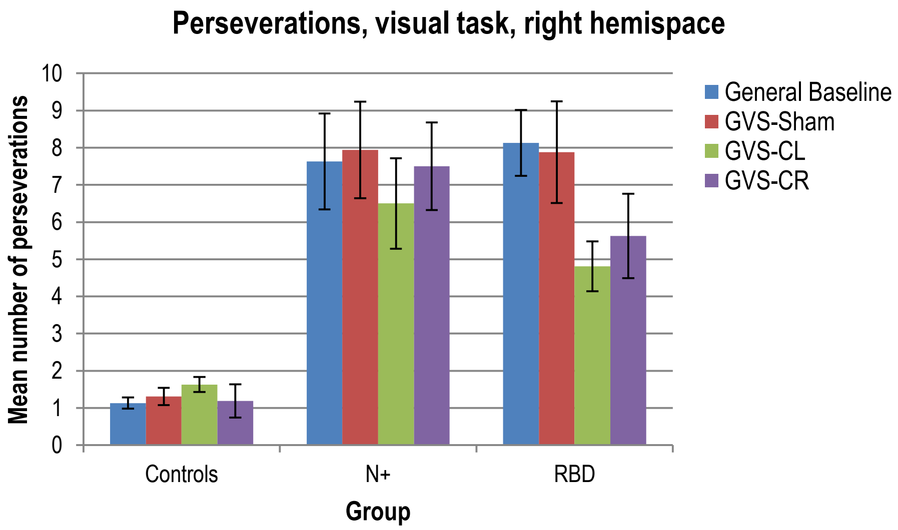

Figure 4.7: Mean numbers (and standard errors of the means) of perseverations in the right hemispace in the visual task for Controls and patient subgroups (Controls, N+, RBD; see text for details).

Significant group differences (Kruskal-Wallis-Tests, df=2, $\alpha = .05$) were found for all GVS-stimulation conditions in left and for all conditions in right hemispace (see Table 4.9 for detailed information).

*Table 4.9: Results (Chi^2, p) of the Kruskal-Wallis-Tests comparing the mean numbers of perseverations in the visual task between the three subject groups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	Chi^2	*p*	*Chi^2*	*p*	*Chi^2*	*p*	*Chi^2*	*p*
left	3,1	.212	7,95	**.019***	8,67	**.013***	6,59	**.037***
right	11,964	**.003***	10,18	**.006***	5,166	**.076***	8,084	**.018***

Paired comparisons (Mann-Whitney-Tests, see Table 4.10) were computed to specify significant differences between groups. Significant differences were found between RBD and controls for GVS-Sham (U=6, p=.005), GVS-CL (U=3, p=.001) and GVS-CR (U=5; p=.003). Note that RBD-group showed worse performance in comparison to both other subject groups.

*Table 4.10: Results (U, p) of paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of perseverations in the left hemispace in the visual task between the three subject groups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	25,5	.505	17,5	.130	20,5	.234	19,5	.195
N+ - Controls	24	.442	19	.195	18,5	.161	27,5	.645
RBD - Controls	14,5	.065	6	**.005***	3	**.001***	5	**.003***

Table 4.11 shows results of paired comparisons (Mann-Whitney-Tests) between groups for right hemispace. Both patient subgroups significantly differ from healthy controls in general baseline (U < 8, p < .01), GVS-Sham (U < 8, p < .01) and GVS-CR (U < 9,5, p < .015). For GVS-CL, only right brain damaged controls significantly differ from healthy controls (U=12, p=.038), while neglect patients do not (U=15, p=.083).

Table 4.11: Results (U, p) of paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of perseverations in the right hemispace in the visual task between the three subject groups (Controls, N+, RBD; see text for details).: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	27,5	.645	29,5	.798	29,5	.798	28	.721
N+ - Controls	8	**.01***	8	**.01***	15	.083	9,5	**.015***
RBD - Controls	0,5	**.000***	4	**.002***	12	**.038***	8,5	**.01***

4.2.4.2 Omissions

4.2.4.2.1 Tactile task

Mean numbers of omissions in the tactile tasks for left (Figure 4.8) and right (Figure 4.9) hemispace.

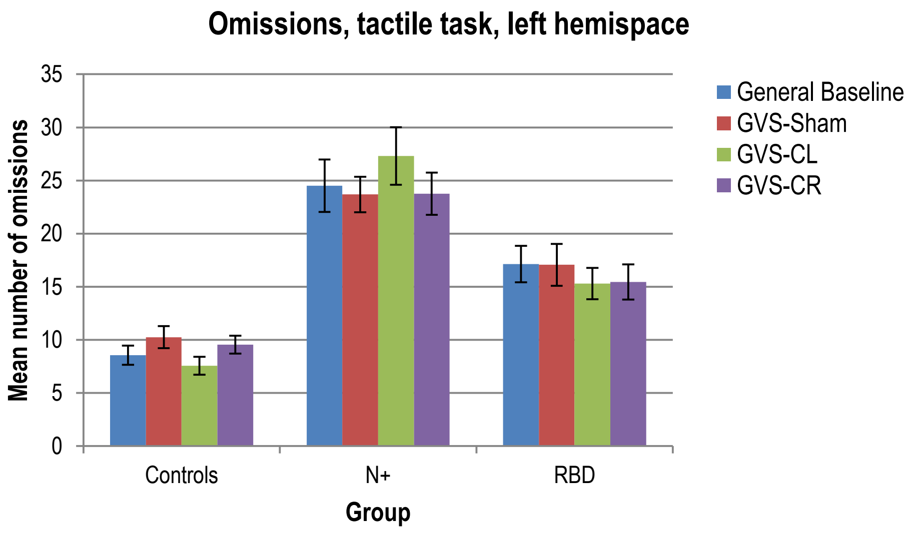

Figure 4.8: Mean numbers (and standard errors of the means) of omissions in the left hemispace in the tactile task for the three subject groups (Controls, N+, RBD; see text for details).

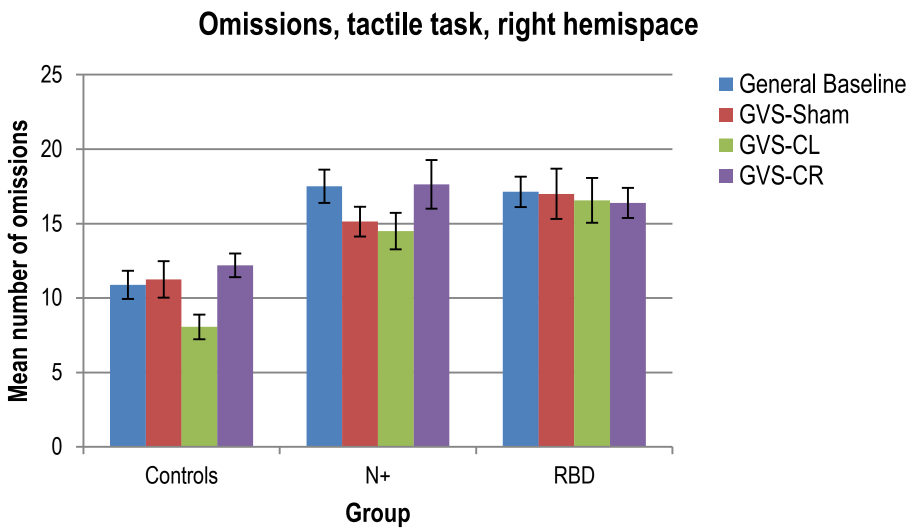

Figure 4.9: Mean numbers (and standard errors of the means) of omissions in the right hemispace in the tactile task for the three subject groups (Controls, N+, RBD; see text for details).

Group comparisons between all subject groups (Kruskal-Wallis-Tests, df=2, α = .05) were calculated regarding experimental conditions (see Table 4.12 for detailed information).

Results indicate significant differences between groups in all conditions concerning left hemispace as well as in GVS-CL for right hemispace.

*Table 4.12: Results (Chi^2, p) of paired comparisons (Kruskal-Wallis-Tests) comparing the mean numbers of omissions in the tactile task between the three subject groups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	Chi^2	*p*	*Chi^2*	*p*	*Chi^2*	*p*	*Chi^2*	*p*
left	7,545	**.023**	6,858	**.032**	9,077	**.011**	7,786	**.020**
right	5,59	.061	2,175	.337	7,369	**.025**	2,371	.306

Concerning left hemispace, paired comparisons (U-Tests, see Table 4.13) revealed significant differences (U <7, p<.007) between N+ and healthy controls in all conditions, showing a clear and typical pattern of neglect associated deficit in the tactile task.

*Table 4.13: Results (U, p) of the paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of omissions in the left hemispace in the visual task between the three subgroups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	23	.382	19,5	.195	17	.130	18	.161
N+ - Controls	6,5	**.005***	7	**.007***	6	**.005***	4,5	**.002***
RBD - Controls	15,5	.083	20,5	.234	14	.065	22,5	.328

Further paired comparisons (U-Tests) were computed for right hemispace (see for Table 4.14 detailed results). While patient groups showed a comparable performance in all conditions (N+ - RBD: $U > 28$, $p > .721$), N+ as well as RBD-subjects performed significantly worse in general baseline (N+ - Controls: $U=12,5$, $p=.038$; RBD – Controls: $U=13$, $p=.05$) as well as in GVS-CL-condition (N+ - Controls: $U=11$, $p=.028$; RBD – Controls: $U=9$, $p=.015$) compared to healthy controls. A visual analysis of the performance of healthy control group suggests a positive effect of GVS-CL in healthy controls, probably leading to a significant result mentioned above. As mentioned above in section [task comparison], healthy controls showed a generally worse performance in the tactile as compared to the visual task.

*Table 4.14: Results (U, p) of paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of omissions in the right hemispace in the visual task between the three subgroups (Controls, N+, RBD; see text for details). *: significant difference (p<.05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	31,5	.959	29	.798	29	.798	28	.721
N+ - Controls	12,5	**.038**	18,5	.161	11	**.028**	21,5	.279
RBD - Controls	13	**.05**	21,5	.279	9	**.015**	17,5	.130

4.2.4.2.2 Visual task

Mean numbers of omissions in the visual tasks for left (Figure 4.10) and right (Figure 4.11) hemispace are shown below.

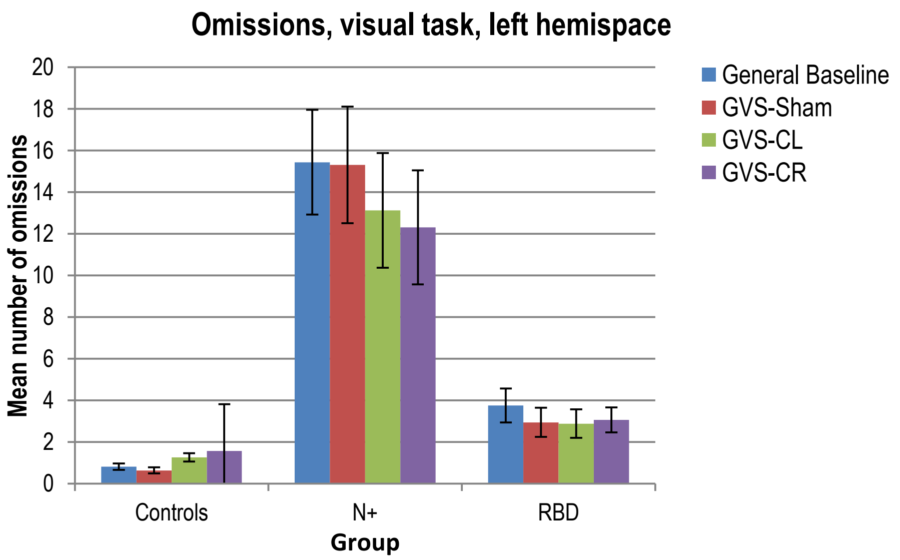

Figure 4.10: Mean numbers (and standard errors of the means) of omissions in the left hemispace in the visual task for the three subject groups (Controls, N+, RBD).

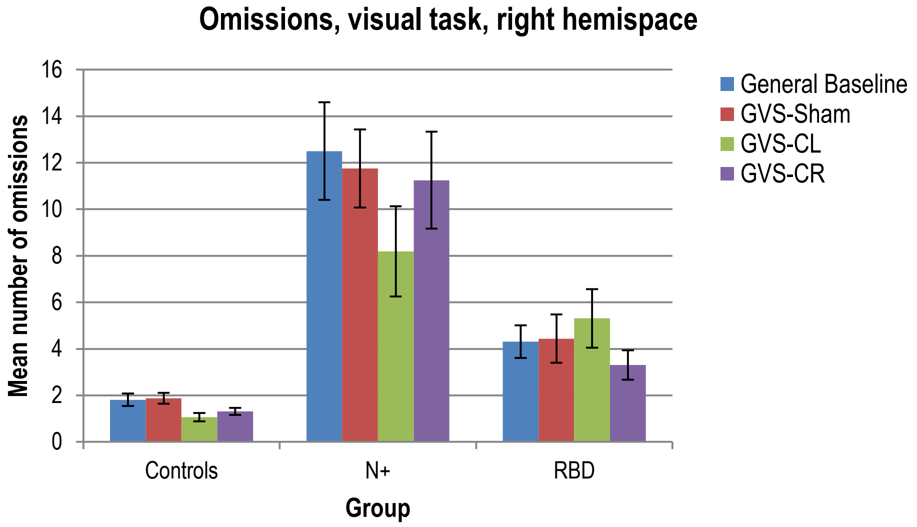

Figure 4.11: Mean numbers (and standard errors of the means) of omissions in the right hemispace in the visual task for the three subject groups (Controls, N+, RBD; see text for details).

Table 4.15 shows the results of the Kruskal-Wallis Tests (df=2, α = .05), separately for left and right hemispace.

Group comparisons (N+, RBD, Controls) showed significant differences between groups in all conditions for left (Chi2 > 7,116, p < .028) and right (Chi2 > 6,623, p < .036).

Table 4.15: Results (Chi^2, p) of paired comparisons (Kruskal-Wallis-Tests) comparing the mean numbers of omissions in the visual task between the three subject groups (Controls, N+, RBD; see text for details).

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	Chi^2	*p*	*Chi^2*	*p*	*Chi^2*	*p*	*Chi^2*	*p*
left	12,537	**.002**	11,376	**.003**	7,116	**.028**	9,367	**.009**
right	6,623	**.036**	9,06	**.011**	6,904	**.032**	7,608	**.022**

For left hemispace, paired comparisons (Mann-Whitney-Tests, see Table 4.16) showed significant differences between neglect patients and both control groups (N+ - RBD: U < 13, p < .05; N+ – Controls: U < 9, p < .015).

Table 4.16: Results (U, p) of paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of omissions in the left hemispace in the visual task between the three subject groups (Controls, N+, RBD; see text for details).

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	9	**.015***	11	**.028***	13	**.05***	12	**.038***
N+ - Controls	0	**.00***	3,5	**.001***	9	**.015***	4,5	**.002***
RBD - Controls	22	.328	16	.105	25	.505	23	.382

Paired comparisons (U-Tests, see Table 4.17) for omissions in right hemispace of the visual task, notably, showed a similar deficit in the neglect group as compared to left hemispace. Neglect patients significantly differed from healthy controls in all conditions (U < 9, p < .015) as well as from patient controls (RBD) in GVS-Sham condition (U=11,5, p = .028).

*Table 4.17: Results (U, p) of paired comparisons (Mann-Whitney-Tests) comparing the mean numbers of omissions in the right hemispace in the visual task between the three subject groups (Controls, N+, RBD; see text for details). *: significant difference (p < .05)*

	Baseline		**GVS-Sham**		**GVS-CL**		**GVS-CR**	
	U	*p*	*U*	*p*	*U*	*p*	*U*	*p*
N+ - RBD	16,5	.105	11,5	**.028**	22,5	.328	17	.130
N+ - Controls	9	**.015**	4,5	**.002**	8	**.010**	6	**.005**
RBD - Controls	21,5	.279	27	.645	16,5	.105	22	.328

4.2.5 Effect of GVS within patient subgroups

4.2.5.1 GVS-effects on patient subgroups

Patient samples (N+, RBD) were separately analyzed concerning their exploration performance in the four experimental conditions (General Baseline, GVS-Sham, GVS-CL, GVS-CR). Table 4.18 shows the results of the

Friedman-Tests (df=3, α = .05) for both patient groups regarding perseverations and omissions in left and right hemispace.

*Table 4.18: Results (Chi^2, p) of the Friedman-Tests comparing the GVS-conditions within patient subgroups (N+, RBD; see text for details). *: significant difference (p < .05).*

		tactile task		visual task	
N+		*Chi^2*	*p*	*Chi^2*	*p*
Perseverations	*Left*	0,432	.932	1,609	.657
	Right	8,25	**.041***	4,040	.222
Omissions	*Left*	0,974	.808	3,696	.296
	Right	2,76	.430	5,883	.117
RBD					
Perseverations	*Left*	2,7	.440	2,316	.509
	Right	0,873	.832	9,446	**.024***
Omissions	*Left*	1,308	.727	1,080	.782
	Right	0,5	.919	0,592	.898

Significant results were analysed using Wilcoxon-Tests (n=8, α = .05).
Neglect patients showed significantly more perseverations in the right hemispace of the tactile task in GVS-CL condition as compared to the baseline condition (Z=+2,51 , p=.012).
In contrast, RBD-subjects showed the reverse pattern for perseverations in their right hemispace of the visual task as indicated in the Friedman-Tests, with marginally less perseverations in the right hemifield under GVS-CL as compared to general baseline performance (Z= -1,823, p= .068).

4.2.5.2 GVS-aftereffects on patient subgroups

Further analyses (Friedman-Tests, df = 3, two-tailed, α=.05, see Table 4.19) between patient samples (N+, RBD) were calculated for exploration performance with respect to GVS-aftereffects as compared to the general baseline (GVS-Sham-AE, GVS-CL-AE, GVS-CR-AE).

*Table 4.19: Results (Chi^2, p) of the Friedman-Tests comparing the GVS-aftereffects to the general baseline condition within patient subgroups (N+, RBD). *: significant difference (p < .05)*

		tactile task		visual task	
N+		*Chi^2*	*p*	*Chi^2*	*p*
Perseverations	*Left*	1,269	.736	1,88	.598
	Right	10,2	**.017***	4,95	.175
Omissions	*Left*	1,885	.597	1,986	.575
	Right	2,55	.466	7,13	.068
RBD					
Perseverations	*Left*	6,75	.80	0,896	.826
	Right	0,154	.985	2,487	.478
Omissions	*Left*	1,35	.717	1,737	.629
	Right	0,154	.985	8,688	**.034***

While neglect patients showed significantly more perseverations in GVS-Sham-AE than in GVS-CR-AE in the tactile task (Wilcoxon-Test, n=8, Z=-2,521, p=.012, see Figure 4.12), RBD-patients showed significantly more omissions in GVS-Sham-AE than in GVS-CR-AE in the visual task (Wilcoxon-Test, n=8, Z=-2,371, p=0.18, see Figure 4.13).

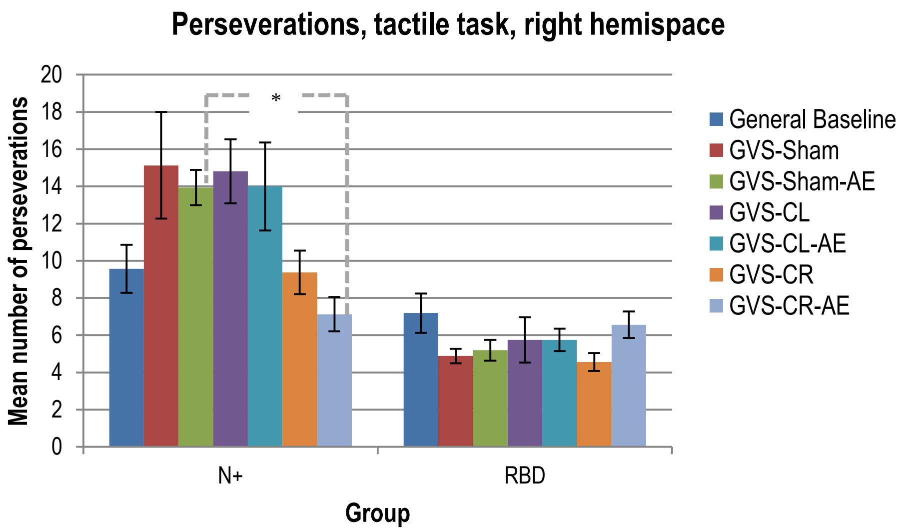

*Figure 4.12: Mean numbers (and standard errors of the means) of perseverations in the right hemispace in the tactile task for the three subject groups (Controls, N+, RBD). *: significant difference (p < .05) in the paired comparison (Wilcoxon-Test; see text for details)*

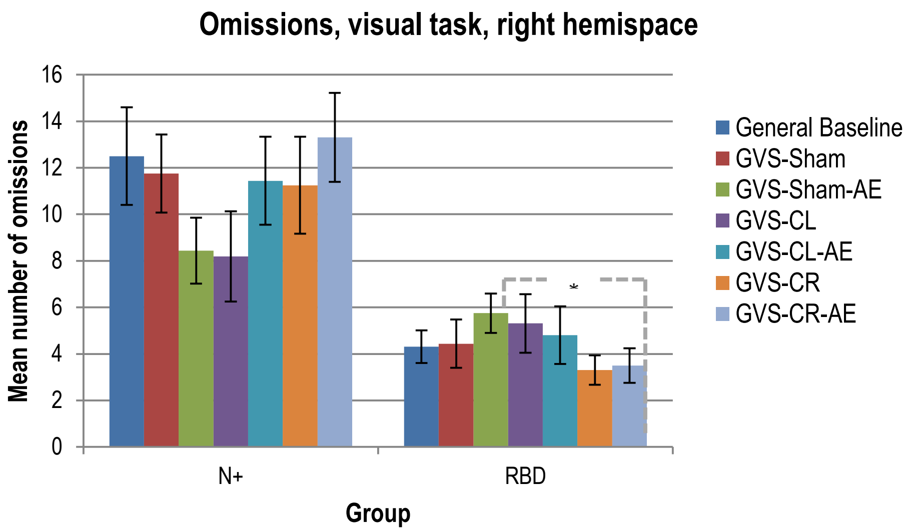

*Figure 4.13: Mean numbers (and standard errors of the means) of omissions in the right hemispace in the visual task for the three subject groups (Controls, N+, RBD). *: significant difference (p < .05) in the paired comparison (Wilcoxon-Test; see text for details).*

4.3 Discussion

Experiment 1 addressed three questions concerning neglect patients' and right brain damaged patients' deficits and their modulation by GVS using the same spatial exploration task in the visual and tactile modalities. The results of these three questions will be discussed in the following consecutively.

4.3.1 Neglect as a multimodal disorder – assessment of multimodal neglect with visual neglect screening tests

In the present experiment, neglect patients and right brain damaged controls were divided in subgroups using standardized visual neglect screening tasks. Patients were assigned to neglect group, if they showed a rightward deviation of the subjective line midpoint in line bisection or if they showed left lateralized omissions in at least one cancellation test. Whereas these screening tests are well known to be eligible to reveal visual neglect, less is known about their ability to distinguish between neglect associated deficits in tactile modality – or in other words, multimodal neglect associated exploration patterns.

Schindler and colleagues (Schindler et al., 2006) found a clear rightward shift of the exploration center with higher omission rates in left hemispace as well as higher repetition rates in both modalities as compared to healthy and right brain damaged controls. Neglect associated deficits seemed to be stronger in the visual than in the tactile task.

Our results obtained with the neglect group and RBD control groups on the basis of the results of the visual neglect screening tests indicate, at least in parts, similar patterns comparing neglect patients' and healthy controls' performance.

As far as omissions are concerned, neglect patients showed the typical neglect associated exploration pattern with significant differences in baseline conditions compared to healthy controls in *both* modalities, with a non-significant lateralization bias for left hemispace. The lack of a significant lateralization bias for left hemifield is probably due to the small sample sizes and associated high standard deviations. Further research with larger sample sizes is needed to evaluate that assumption in more detail.

In case of repetitions in the visual task, neglect patients showed significantly higher repetition rates in right hemispace as compared to healthy controls as well as at least more (but not significantly more) perseverations in the left hemispace, while they did not show higher repetition rates in baseline condition of the tactile task in any hemifield. The latter fact could be due to several aspects. First, healthy controls showed even higher perseveration rates in the left hemifield of the tactile task than neglect patients do. This could be caused by higher omission rates and a rightward shift of the exploration center leading to a smaller perseveration rate of neglect patients in the left hemifield, because they do not search there. Secondly, healthy controls showed significantly worse performance in all tactile task conditions as compared to the visual conditions, indicating a clear difference of task difficulty for healthy controls. This is probably aggravated by a ceiling effect in the visual test condition. Taking into account the small sample sizes and associated high variability (standard deviations and error variances), there could be additional peculiarities concerning tactile search behavior of healthy controls in this experiment. Hence, further research with larger sample sizes is needed to clarify this point in more detail.

4.3.2 Modality specific associations and dissociations within the patients' subgroups

The second aspect of multimodality addressed in the present experiment is modality specific differences. As mean perseverations and omissions in Wilcoxon comparisons (see Table 4.5) within subgroups indicate, there are differences concerning task modality (see Figure 4.14 and Figure 4.15).

Whereas healthy controls show a clear advantage in visual tasks for both perseverations and omissions, neglect patients as well as right brain damaged controls differ only with respect to omissions in task modality, but not with respect to perseverations. Put differently, repetitive search behavior was not affected by task modality, but comparable in both modalities in these patients. This could be interpreted as a general, modality unspecific exploration deficit in neglect patients as well as right brain damaged control patients, leading to a consistent pattern of poor spatial exploration without any effect of modality.

Whereas perseveration behavior seems to be similarly affected in neglect patients and right brain damaged controls, another tendency seems to apply to omissions. While RBD patients show significant differences between visual and tactile performance in left and right hemispace, neglect patients significantly differ only in left hemispace with respect to modality. This difference between patient subgroups may indicate the global exploration deficit mentioned above with an additional effect of neglecting behavior in left hemispace for neglect subgroup, resulting in an additional negative effect on exploration performance compared to RBD control patients, which show exploration patterns similarly to healthy controls. These results are in line with findings of Olk & Harvey (2006), who compared visual and tactile search in right brain damaged patients with and without neglect, additionally varying task difficulty (by means of task modality and number of relevant targets). They did not find any effect of target number on exploration performance (Olk & Harvey, 2006). They interpreted this result as being due to the high demands of the search process itself, irrespective of task difficulty and memory load for *both* patient groups. This effect was also seen in our samples, with significant differences between visual and tactile search in healthy controls but not consistently in patient subgroups.

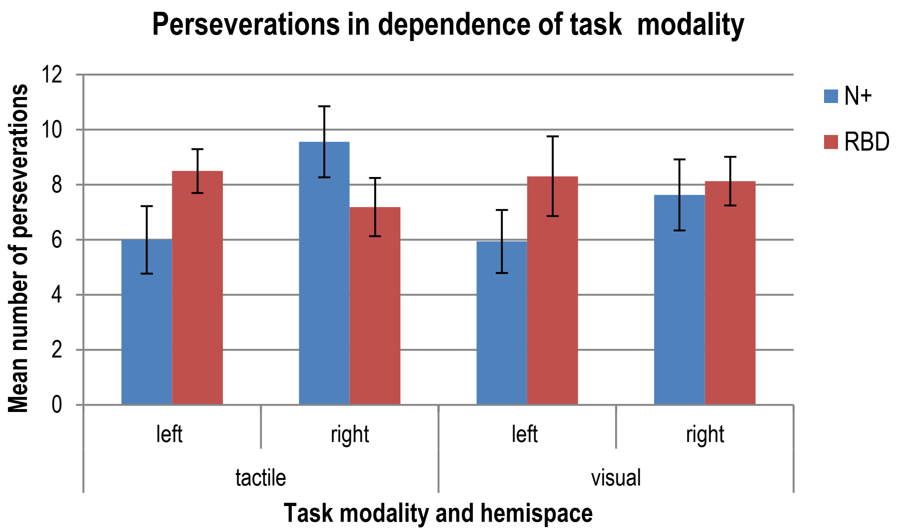

Figure 4.14: Mean numbers of perseverations (and standard errors of the means) in left and right hemispace comparing the visual and the tactile task in patient subgroups (N+, RBD; see text for details).

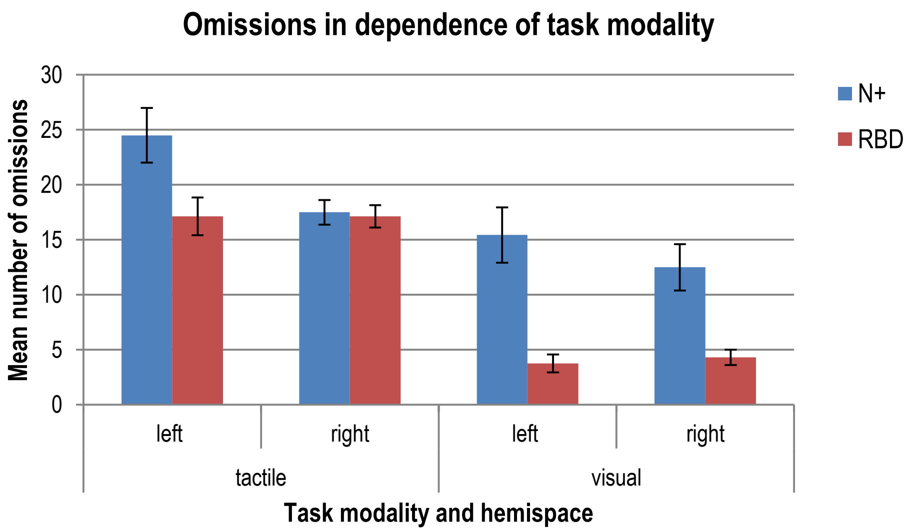

Figure 4.15: Mean numbers of omissions (and standard errors of the means) in left and right hemispace comparing the visual and the tactile task in patient subgroups (N+, RBD; see text for details).

4.3.3 Multimodal search deficits in right brain damaged patients with and without neglect

The present exploration task, based on the paradigm of Schindler and colleagues (Schindler et al., 2006), allows a direct comparison between visual and tactile exploration performance in neglect patients and right brain damaged controls in comparison to healthy controls. As already mentioned above (see section 2.2), there is some evidence, that right brain damaged controls do not always perform on the same level as healthy controls, but show some residual exploration deficits regarding repetitive search (Ronchi et al., 2012; Schindler et al., 2006; Olk & Harvey, 2006; Pia et al., 2009).
Our data also suggest deficits in exploration behavior not only in right brain damaged patients with but also those *without* neglect.

As far as omissions in the tactile task are concerned, right brain damaged patients showed an omission rate which, in fact, was *between* those of neglect patients and healthy controls in left hemispace, not significantly differing to any of those groups, and, interestingly, significantly more omissions in right hemispace comparing to healthy controls – on a comparable level to neglect patients.
These results concerning tactile exploration are comparable to that of Haeske-Dewick and colleagues (Haeske-Dewick et al., 1996), who found higher omission rates in far left hemispace compared to healthy controls only in the tactile task, interpreted as a form of “residual neglect” or “partial recovery”, but *not* in the visual modality. Results of the present study can be interpreted in line with this assumption, indicating residual deficits in the tactile task due to a limitation of using compensatory strategies orienting attention intentionally leftwards.
Notably, in the visual task, right brain damaged controls only differ significantly from neglect patients in left hemispace, but not in right. For left hemispace, the neglect associated, high omission rate in the neglect group leads to significant differences between patient groups. Omission rates in right brain damaged controls in right hemispace are, in fact, not significantly different from *neither* healthy controls *nor* neglect patients in right hemifield, resulting

again in a pattern of exploratory deficits ranging *between* performances of neglect patients and healthy controls.
These results emphasize again residual exploration deficits in right brain damaged controls.

Repetitive search was also different across modalities in right brain damaged controls.
Interestingly, there were no significant differences in baseline conditions between any groups in the tactile task. This result could be explained considering several aspects. First, as already mentioned above, tactile task seemed to be much harder for healthy controls than visual task, leading to overall higher perseveration rates in that group, reaching a level comparing to that of patient subgroups. This could be interpreted as a special feature of our small healthy control sample or a statistical artifact, induced by high error variances, or it can be assumed to be caused by the nature of the tactile task. Furthermore, search itself seems to be challenging for patient subgroups irrespective of task modality, in line with other findings in the literature (Olk & Harvey, 2006; Rusconi et al., 2002).
Furthermore, perseveration rates in neglect patients are slightly lateralized with lower rates in left and higher rates in right hemispace, while there is no such effect in right brain damaged or healthy controls, in line with previous research (Pia et al., 2009; Rusconi et al., 2002), depicting the typical neglect associated perseveration pattern at least a kind of tendency (Schindler et al., 2006; Rusconi et al., 2002; Haeske-Dewick et al., 1996). Hence, larger samples are needed to specify that observations concerning repetitive search, additionally with respect to potentially associated brain regions, namely the influence of right brain damage in basal ganglia (Pia et al., 2009).
In the visual task, the typical repetitive patterns mentioned above are seen in both hemifields. Neglect patients show slightly more perseverations in right than left hemifield, while right brain damaged controls show consistently higher perseveration rates in both hemifields compared to healthy controls, whereas those differences reach a significant level only in right hemispace. These results go in line with findings of Pia and colleagues (Pia et al., 2009),

who found repetitive search rates on a comparable level between patient subgroups.

Comparison of visual versus tactile perseveration rates leads to similar patterns found in the study of Schindler et al. (Schindler et al., 2006), who found overall higher repetition rates in the tactile task as well as a slight lateralization effect in neglect group, which is not consistently found in right brain damaged controls (for detailed information, see Schindler et al., 2006, Figure 2, page 1447).

Overall, these results indicate explorative deficits in right brain damaged controls, which seem to be associated with right brain damage per se, probably depicting an “instability of space representation” (Rusconi et al., 2002) even in the absence of manifest left spatial neglect. This deficit may be viewed as a kind of independent component in exploration tasks (Ronchi et al., 2012; Ronchi et al., 2009; Pia et al., 2009). More research with larger sample sizes is needed to evaluate these findings in greater depth.

4.3.4 Effect of GVS between and within samples

Fink and colleagues (Fink et al., 2003) as well as some recent studies (Schmidt et al., 2013a; Utz et al., 2011b; Oppenländer et al., 2015; Schmidt, Utz, Depper, Adams, Schaadt, & Reinhart, 2013b) suggest galvanic vestibular stimulation as a promising technique for modulation of neglect and associated deficits.

The present study addressed, among others, a potentially ameliorating effect of galvanic vestibular stimulation on visual and tactile exploration in right brain damaged patients with and without neglect.

Within group comparisons for the two patient subgroups did not reveal any ameliorating effect of GVS on exploration behavior concerning omissions or perseverations for neglect patients. Right brain damaged controls, though, showed significantly less perseverations in their right hemifield in the visual task as compared to baseline performance, indicating a potentially ameliorating effect of GVS on perseverations. This result was in contrast to that of neglect patients, who showed significantly *more* perseverations in their right hemifield of the tactile task when compared to baseline performance. This inconsistent effect is not explainable with respect to the present literature and should be interpreted with caution because of the small sample sizes and high error variances.

Graphical analyses of the mean numbers of omissions and perseverations suggest a probably ameliorating tendency of GVS for neglect patients under left cathodal / right anodal stimulation concerning perseverations in the left hemifield as well as for omissions in both halves of the exploration table in the visual task as well as well as only for right lateralized omissions in the tactile task. Further research is necessary to evaluate these findings in more detail with larger samples.

Further limitations of the present study, additionally to the small sample sizes, should be mentioned which could probably account for the lack of a positive therapeutic effect of GVS on the exploration behavior in neglect patients. Firstly, patient samples showed some heterogeneity concerning time since lesion (ranging from 1 to 152 months) as well as lesion anatomy. A subdivision of acute vs. chronic states of impairments as well as more homogenous lesion locations could probably reduce the error variance induced by factors which were irrelevant but also uncontrollable in the present study.

Secondly, the nature of the task used in the present investigation could account for the lack of any statistically evaluable effect. Comparing to standardized exploration tests, e.g. cancellation tasks, the exploration board used here is much larger, resulting in a higher complexity as well as a higher number of stimuli, increasing variability of search performance between subjects. Additionally, constraints concerning mobility and flexibility of upper extremities may influence tactile search performance.

4.3.5 Limitations

There are some limitations concerning the present study.

First, as already mentioned above, further research with larger and more homogenous samples is needed to evaluate these findings described above in more detail. Current results should be interpreted with caution, in sense of tendencies.

Additionally, in the present exploratory study, no correction for alpha error was set (Bonferroni- or Holmes procedures). Hence, further research using the present paradigm with larger sample sizes is needed using directional hypotheses based on the present data to analyze specific aspects of exploration behavior.

5 Experiment 2 – Effects of head-on-trunk modulation on auditory neglect

Many aspects of multimodal neglect, such as visual, tactile or representational neglect, can be modulated by sensory stimulation or cognitive manoeuvres (Vallar, Guariglia, & Rusconi, 1997; Rossetti & Rode, 2002; Robertson & Manly, 2002; Kerkhoff, 2003; Kerkhoff & Schenk, 2012). Less is known about modulating factors in auditory neglect (for detail, see section 2.3).

Previous studies in normal subjects indicate that neck proprioceptive input (Lewald, Karnath, & Ehrenstein, 1999) and head-on-trunk-position (Lewald & Ehrenstein, 1998; Goossens & Van Opstal, 1999) modulate auditory lateralization and localization performance. In studies with neglect patients it was shown that neck-proprioceptive input induced by mechanical vibration of the contralesional neck muscles reduced the degree of visual neglect considerably (Karnath et al., 1993; Karnath, Fetter, & Dichgans, 1996). Similar beneficial effects have been observed with the experimental modulation of the lateral head-on-trunk-position in patients with visual neglect (Schindler & Kerkhoff, 1997; Fujii et al., 1996; Vuilleumier et al., 1999)

In the following two experiments, the modulating effect of head-on-trunk-position on auditory neglect as assessed by localization and identification tasks sensitive to spatial neglect was assessed.

Experiment 2a addressed the question, whether the manipulation of the head-position (leftward, rightward or straight ahead) on the stationary, upright trunk influences sound localization, assessed by the perceived auditory subjective median plane (ASMP) in patients with visual and auditory neglect, non-neglecting patients with unilateral brain damage and normal subjects in their horizontal front space.

In Experiment 2b, however, investigated the influence on head-on-trunk-position on sound identification performance in neglecting and non-neglecting patients and healthy controls.

5.1 Experiment 2a – Localization task

5.1.1 Methods

5.1.1.1 Subjects

The clinical and demographic data of the three subject groups tested is given below (Table 5.1, Table 5.2): 8 patients showed left sided visual neglect after a unilateral right sided lesion (termed "N+"; mean age 51,1 years; SD 10,2). The patient control group included another 8 patients who had suffered from unilateral left or right lesions without contralesional visual neglect (termed "RBD": mean age 48,6 years; SD 13,4). Eight healthy control subjects (termed "Controls") of the same age were matched to these two patient groups. All subjects had normal hearing sensitivity according to pure-tone audiometry (Figure 1, see below). The three subject groups did not differ according to age (Kruskal-Wallis-Test, Chi-square=1.229, df=2, $P > 0.05$) and the two patient groups did not differ in their time since lesion (Mann-Whitney-U-Test; $Z=-.636$, $p=0.574$). All patients showed sufficient verbal comprehension in order to understand the instructions of the tasks (especially in the patient control group where 2 patients showed residual aphasia).

Table 5.1: Clinical and demographic data of 8 patients with right-hemispheric lesions and left sided visual neglect (N+) in Experiment 2a. Abbreviations: f: female, m: male; R: right, L: left; TSL: Time since lesion (in months); Lesion Loc.: Lesion localizationICB: intracerebral bleeding; MCI: middle cerebral artery infarction; AV: arteriovenous malformation, operated; TU-OP: tumour, operated; BG: basal ganglia; occ, par, temp, front: occipital, parietal, temporal, frontal; Bisection: the deviation from the true midline is given (in mm); Copy: copy of a star: -: left sided omissions or size distortions, +: normal copy on right side of figure; Cancell.: cancellation of 30 numbers embedded in 200 distractors: L/R: the number of left/right sided omissions is given. Reading: text of 180 words, irregularly indented on both margins. SD: standard deviation

Code	Age Sex	Etiology	TSL	Lesion Loc.	Field defect (°)	Bisect	Copy L/R	Cancell. L/R	Reading
N1	57,f	MCI	13	right-par	Hemianopia, 3°	+10	-/+	+/-	Normal
N2	53,m	MCI	2	right-BG	Normal	+28	-/+	+/-	impaired
N3	63,f	TU-OP	5	right-temp	Normal	+26	-/+	+/+	impaired
N4	31,f	AV	12	right-temp	Normal	-2	-/+	-/-	impaired
N5	59,m	MCI	3	right-par	Normal	+40	-/+	+/-	impaired
N6	44, f	MCI	12	right-par	Hemianopia, 30°	+8.5	-/+	+/-	impaired
N7	47, f	MCI	2	right-par	Normal	+8	-/+	+/-	Normal
N8	55,m	ICB	8	right-front-par	Normal	+32	-/+	+/+	impaired
Mean	**51.1 yrs (SD 10,2)**		**7,13 (SD 4,73)**	**--**	**---**	**+18.8mm**	**---**		**---**

Table 5.2: Clinical and demographic data of 8 patients with right-hemispheric lesions and without left sided visual neglect (RBD) in Experiment 2a. Abbreviations: f: female, m: male; R: right, L: left; TSL: Time since lesion (in months); Lesion loc.: Lesion localization; ICB: intracerebral bleeding; MCI: middle cerebral artery infarction; TU-OP: tumour, operated; Thal: Thalamus; BG: basal ganglia; temp, front: temporal, frontal; Bisection: the deviation from the true midline is given (in mm); Copy: copy of a star: -: leftsided omissions or size distortions, +: normal copy on right side of figure; Cancell.: cancellation of 30 numbers embedded in 200 distractors: L/R: the number of left/right sided omissions is given. Reading: text of 180 words, irregularly indented on both margins. SD: standard deviation

Code	Age, Sex	Etiology, TSL	Lesion Loc.	Field Defect (°)	Bisect.	Copy L/R	Cancell. L/R	Reading
RBD9	25,f	ICB, 3	R-Thal	normal	+3	+/+	-/-	Normal
RBD10	57,m	ICB,7	R-BG	normal	0	+/+	-/-	Normal
RBD11	53,f	TU-OP, 5	R-temp	Quadrantanopia 55°	0	+/+	-/-	Normal
RBD12	61,m	MCI,3	L-temp	normal	-3	+/+	+/+	Aphasia
RBD13	55,m	MCI,5	L-temp	normal	+5	+/+	-/-	Aphasia
RBD14	30, f	ICB, 4	L-BG	normal	+2	+/+	-/-	Aphasia
RBD15	51, f	MCI, 7	R-BG	normal	- 2	+/+	-/-	Normal
RBD16	57,m	MCI,4	R-front	normal	-7	+/+	-/-	Normal
Mean	**48.6 yrs (SD 13,44)**	**TSL: 5,94 (SD 1,58)**	**---**	**---**	**- 0.25 mm**	**---**		**---**

5.1.1.2 Visual neglect tests and visual field testing

Neglect patients were identified on the basis of four conventional visual neglect tests: horizontal line bisection of a 20 x 1 cm black line on a white sheet of paper (Schenkenberg et al., 1980); number cancellation (Wilson, Cockburn, & Halligan, 1987) with 30 targets among 150 distractors, presented on a 29.7 x 21 cm large white paper; drawing of a clock face (Kerkhoff, 2000), and an indented reading test of 180 words (Kerkhoff, Wimbauer, & Reinhart, 2012).

Neglect was diagnosed when the truncation midline in bisection deviated more than 5 mm to the ipsilesional side, when more than one target was omitted on the left side in number cancellation, when numerals were omitted or misplaced on the left side of the clock face test, or when the subject committed more than two reading errors (for details, see Schindler & Kerkhoff, 2004). Binocular visual fields were mapped perimetrically with a Tübingen or Goldmann perimeter in all patients (for more details of these screening tests see Kerkhoff, 2000).

5.1.1.3 Peripheral (monaural) hearing tests

All subjects except one control patient were screened with a Philips HP 8741/31 pure-tone audiometer for peripheral (monaural) hearing functions in a sound-shielded room. Hearing sensitivity (loss in dB) was measured in each ear for the following frequencies: 0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 kHz. Subjects with ear or vestibular disease were excluded.

5.1.1.4 Auditory subjective median plane (ASMP)

Auditory stimuli were broad-band (white-noise), 3 s single-pulse signals (sound pressure level, SPL: 75 dB, as measured by a Brüel & Kjaer audiometer). They were delivered sequentially by an AKG K240 headphone with a frequency range similar to that used in the HRTF-measurements (see below). Signal pulses were passed through digital linear minimum phase filters (FIR-filter design) with direction-dependent head-related transfer functions

(HRTF, Wenzel, Arruda, Kistler, & Wightman, 1993; Wightman & Kistler, 1989a; Wightman & Kistler, 1989b) to simulate virtual sound locations of a 5° resolution in the horizontal front space. HRTF-parameters used for binaural simulation were derived from dummy-head measurements which contained interaural and monaural auditory directional cues and were normalized with respect to an average across all directions to minimize the influence of the measurement system and ear channel response. Figure 5.1 demonstrates the experimental paradigm used in the present study.

- Aus Datenschutzgründen entfernt -

Figure 5.1: Layout of the task for determining the auditory subjective median plane (ASMP, see text for details): Source: Kerkhoff et al. (2012), Neuropsychologia, 50, Figure 1A, page 1167.

There were 37 sound source directions in front space (including the objective midline position at 0°). The starting positions of the stimuli were pseudo-randomized across these 37 possible directions. One to two trials were presented for each source position so that starting positions from the left and right hemispace were balanced. The subject was seated at a distance of 0.35 m centrally in front of a black computer monitor (luminance: < 1 cd/m2), on which a yellow fixation spot (0.5° diameter, luminance: 20 cd/m2) was presented on a black background. Apart from this fixation spot, the testing room was completely dark. Head position was stabilized by a head- and chinrest whereas the trunk remained fixed straight ahead to the fixation point on the screen in all conditions of both experiments. Subjects were instructed to indicate as accurately as possible whether an acoustic stimulus came directly from the auditory subjective median plane (ASMP) position, or whether it had to be shifted to the left or right until the ASMP was reached. The ASMP was defined as the subjectively perceived median plane in relation to the body sagittal. Twelve practice trials were given after explanation of the task (which were not scored). No time constraints were imposed on the subjects during the measurements. All experimental conditions were run on separate days, in order to exclude possible aftereffects of eccentric head positions on subsequent tests (cf. Day & Wade, 1966; Lackner, 1973).

Normative data for this task obtained from 22 healthy subjects, which were tested with the same system, testing room and with their head and trunk straight ahead, indicate that subjects center their ASMP judgments in front space close to the veridical 0°-direction (mean: -1.9° to the left; maximal range: -7.6° to the left up to +3.3° to the right (Kerkhoff et al., 1999).

5.1.1.5 Experimental conditions

The ASMP task was performed under three experimental conditions the sequence of which was pseudo-randomized among subjects: a) baseline condition with the head straight (0°) in the head- and chinrest, and the trunk oriented straight ahead in an experimental chair; b) leftward passive rotation (20°) of the subject´s head while the trunk remained straight ahead in the chair; c) rightward rotation of the subject´s head (20°) while the trunk remained oriented straight ahead towards the fixation spot on the screen. Head position was changed by the experimenter without any active movement of the subject. Note, that the auditory input was identical in all three experimental head-conditions because it was delivered via head-phones.

5.1.1.6 Data analysis

First, a three-way multivariate analysis of variance for repeated measurements for peripheral monaural hearing tests (hearing acuity) with “frequency” (0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 kHz) and “ear” (left / right) as within factors and “group” as between factor was calculated to approve there were no significant differences in hearing acuity between subject groups.

Mean ASMP were analyzed with an ANOVA for repeated measures with subject group as between-subjects-factor and head condition as within-subjects-factor. Post-hoc t-tests (2-tailed, Bonferroni-corrected) were computed as paired comparisons of the residual angle between subgroups, and dependent post-hoc t-tests (2-tailed, Bonferroni corrected) for neglect group were used as paired comparisons regarding the effect of head rotation.

5.1.2 Results

5.1.2.1 Peripheral (monaural) hearing tests

Figure 5.2 summarizes the results of the peripheral (monaural) hearing tests in the three subject groups. Analysis of variance for repeated measurements (ANOVA) revealed a significant effect of frequency ($F(10, 12)=27.045$, $p<0.0001$), but no significant group effect for ear $F(1, 21)=0.170$, $p>0.05$), nor a significant ear-by-group interaction ($F(2, 21) =1.98$, $p>0.05$), frequency-by-group-interaction ($F(20, 26)=1.588$, $p>0.05$), nor a three-way ear-by-group-by-frequency-interaction ($F(20, 26)=0.554$, $p>0.05$). Hence, the three subject groups showed comparable peripheral hearing functions, and no group showed any significant difference in hearing acuity between the left and right ear which possibly could produce shifts in the ASMP. The significant frequency effect was not pursued further since the well-known sensitivity decline with higher tone frequencies occurred in all three subject groups and was unrelated to the present study.

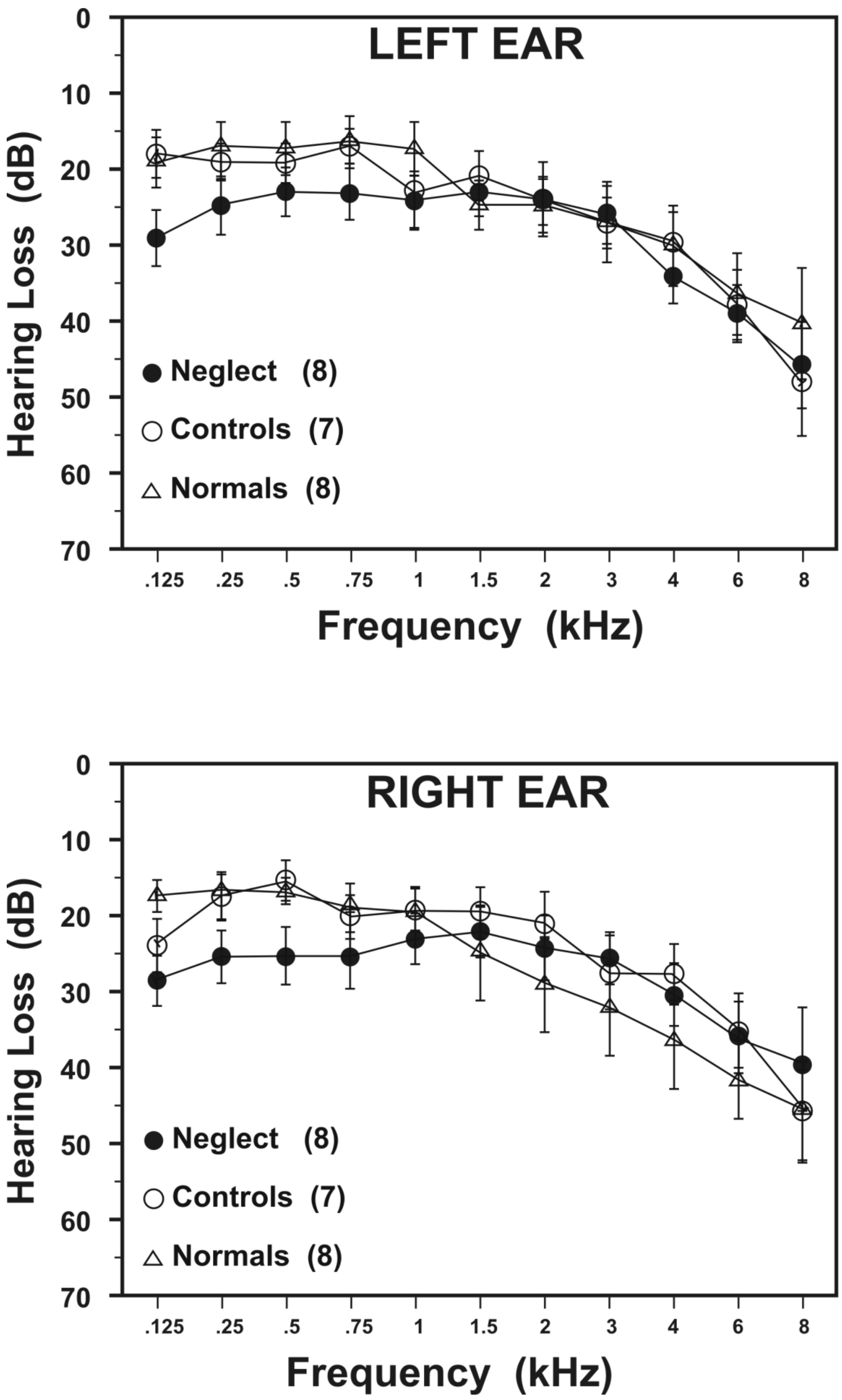

Figure 5.2: Mean (and standard error of the mean) hearing loss (in dB) in three subject groups in pure-tone audiometry for the left and right ear. Apart from the typical decline for high-frequency sounds in all subject groups no significant group or ear differences were obtained (see text for details).

5.1.2.2 Auditory subjective median plane (ASMP)

Figure 5.3 displays the mean residual angles (plus the 95% confidence interval) of each subject over the three head conditions when the subject finally indicated that the auditory stimulus coincided with his/her subjectively perceived ASMP in front space. ANOVA for repeated measures of the mean ASMP (with subject group as between-subjects-factor and head condition as within-subjects-factor) revealed a significant main effect for subject group ($F(2, 20)=17.071$, $p<0.0001$) and head condition $F(2, 20)=37.417$, $p<0.0001$), as well as a significant interaction between both factors ($F(4, 42)=47.576$, $p<0.0001$).

Post-hoc t-tests (2-tailed, Bonferroni-corrected revealed that the neglect patients differed in their residual angle in the baseline condition significantly from the normal subjects ($p<0.0001$), and the control patients ($p<0.0001$) while the latter two groups did not differ significantly ($p>0.05$).

Post-hoc, dependent t-tests (2-tailed, Bonferroni corrected) in the neglect group revealed that leftward head shifts led to a significant shift of the neglect patients´ ASMP towards their left, previously neglected hemispace as compared to the baseline condition ($t=5.964$, $p<0.0001$) so that they were not different from the normal subjects in this condition ($p>0.05$), and scored slightly farther to the left, previously neglected side as the control subjects ($p<0.05$). Normal and control subjects again did not differ in their auditory performance under leftward head orientation ($p>0.05$).

Rightward head orientation significantly shifted the ASMP of the neglect patients towards their right, ipsilesional hemispace as compared to leftward head orientation ($t=-13.508$, $p<0.0001$) but did not differ from the head straight condition ($t=-0.588$, $p>0.05$). As in the head straight condition the neglect patients differed significantly from both the normal ($p<0.05$) and the brain lesioned control subjects ($p<0.05$) during rightward head orientation.

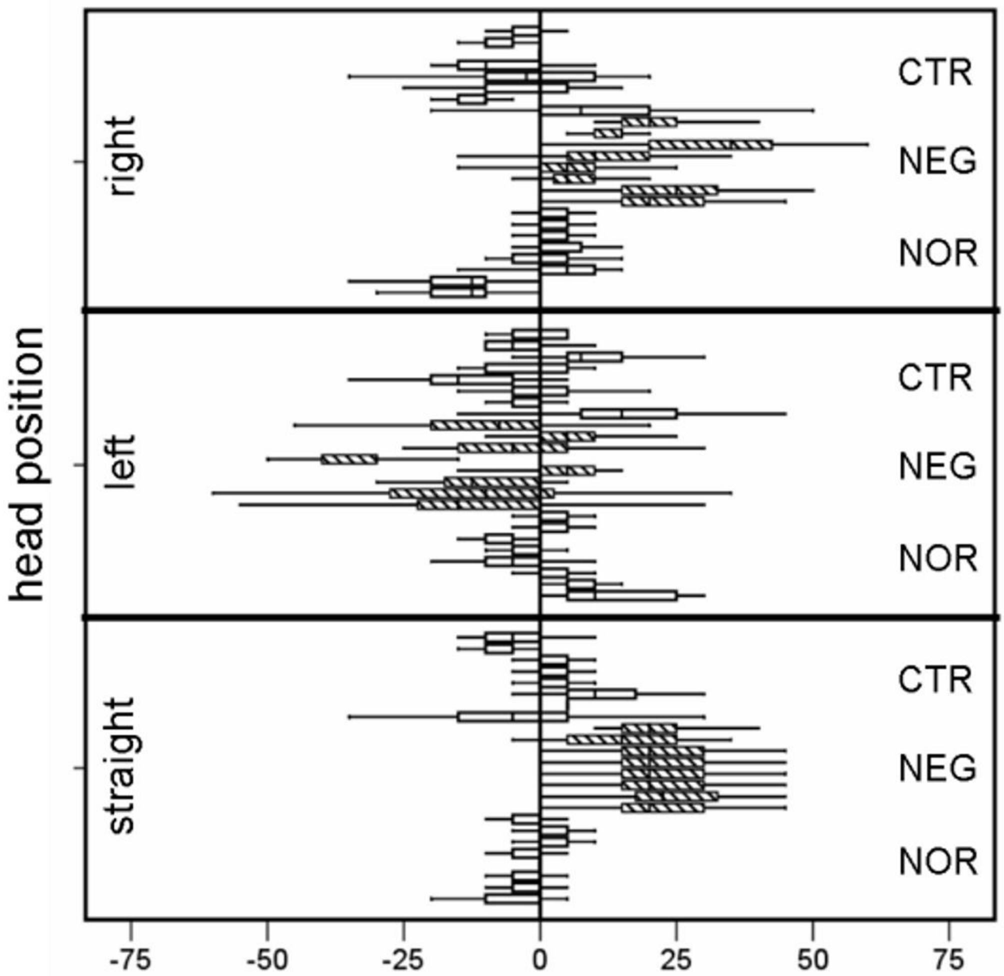

Figure 5.3: Mean residual angle (+/- 95% confidence interval=error bars) of each subject in the auditory subjective median plane (ASMP, exp. 2a) under three head-on-trunk-positions (head straight=baseline, head left=head rotated to the left by 20°, head right=head rotated to the right by 20°). The trunk was oriented straight in all conditions. The open bars on top of each of the three subfigures depict the performance of the 8 control patients without spatial neglect, the striped bars in the middle of each of the subfigures that of the 8 neglect patients, and the open, white bars the data of 8 normal subjects. Each bar shows the data of one subject. Note the significant ipsilesional, right sided shift of the ASMP during head straight and head right selectively in the neglect patients, and the leftward relocation of the ASMP by leftward head rotation. Note that the shift of the ASMP in the non-neglecting and normal subjects is smaller in magnitude and in most cases opposite to the direction of the head-rotation.

Table 5.3 summarizes the graphic data of Figure 5.3 in numerical form and gives mean values and standard deviations for each group and experimental condition. This again shows that the modulating effect of leftward head orientation was quite strong in the neglect group when compared against the head straight condition (on average 18-25° of improvement in the ASMP). In contrast, the effects of eccentric head position in the two other groups fall in two categories: a) a small subgroup in both subject groups adjusted their ASMP during eccentric head position in the direction of the head rotation and b) the larger subgroup adjusted the ASMP opposite to the direction of head rotation (see Figure 5.3).

Table 5.3: Mean results (standard error of the mean) of the three subject groups in the auditory subjective median plane (ASMP, in degrees) in experiment 2a (pooled data from Figure 5.3) across the three experimental head-on-trunk-positions (see text for details). + denotes deviation to the right side, - denotes deviation to the left side of the objective median position. Subject groups are the same as in Figure 5.3.

Experimental Condition	Patients with left neglect (N=8)	Control patients without neglect (N=8)	Normal Subjects (N=8)
Head Straight (Baseline)	+18.5 (0.9)	0.5 (2.1)	-1.7 (0.9)
Head Left (20°)	-8.8 (3.9)	0.6 (3.3)	1.5 (2.4)
Head Right (20°)	+ 16.6 (3.4)	-2.5 (2.3)	-1.7 (2.7)

5.1.3 Discussion

The following results were obtained in experiment 2a: 1) leftward, contralesional head orientation leads to a significant relocation of the perceived ASMP into the normal range (in 4 patients) or even to far to the left, previously neglected hemispace (in the other 4 patients); 2) during rightward head orientation and head straight the neglect patients show a similar pathological shift of the ASMP towards the ipsilesonal side; 3) Normal subjects and control patients without multimodal neglect show small localization errors with eccentric head orientation which in general are opposite to the direction of the head orientation; 4) Our results obtained with the binaural simulation approach of sound localization in neglect are compatible with the results of earlier studies using dichotic (Bisiach et al., 1984), free field auditory stimulation in front space (Vallar et al., 1995) or binaural simulation stimuli (Tanaka et al., 1999) thus confirming the validity of our binaural measurement technique.

Why does head position strongly affect auditory performance in the neglect group but shows only small deviations in the opposite direction in the non-neglecting patients and normal subjects? First, this suggests that the position of the head in relation to the trunk and the auditory information were “merged” in a different way in neglecting versus non-neglecting subjects. We suggest that this differential multisensory integration reflects an imbalance between auditory and head-on-trunk-information caused by the lesion that led to the multimodal neglect. In contrast, left or right hemispheric lesions that do not lead to multimodal neglect caused no or even less imbalance between different sensory space maps, and therefore these patients show only small effects of eccentric head-on-trunk-position. The results of the control patients and healthy control subjects are essentially similar and agree with previous studies of audio-spatial localization under eccentric head position in healthy subjects (Day & Wade, 1966; Lackner, 1973).

The strong modulatory effects of head-position within a rather short time period (5-10 minutes) indicate that the shifted representation of auditory space may be dynamically updated by the information relating the head to the body sagittal within a few minutes. In line with many other studies (cf. Vallar et al., 1997) we found that ipsilesional head orientation had no further deteriorating effect as compared to the head-straight condition. This may be explained by the hypothesis that the ASMP in many of our neglect patients already showed a maximum ipsilesional deviation to the right side which could not be shifted further.

5.2 Experiment 2b – Identification task

While the effects of experiment 2a quite clearly demonstrated the effect of head-on-trunk-position in an explicit auditory spatial localization task, one might ask whether this effect of head-on-trunk-position extends to other auditory tasks as well. Some anatomic (Romanski et al., 1999), imaging (Maeder et al., 2001) and neuropsychological studies with brain lesioned patients (Bellmann et al., 2001; Clarke et al., 2000; Maeder et al., 2001; Clarke & Bellmann Thiran, 2004; Eramudugolla & Mattingley, 2009), suggest a similar segregation of spatial and feature (or object-related) processing in the auditory system as found in the visual modality (Ungerleider & Mishkin, 1982; Ungerleider & Haxby, 1994). As in vision, auditory localization and identification may be the respective specializations of the dorsal and ventral auditory system (for detail, see section 2.3). This led to the question whether the facilitatory effect of leftward head-on-trunk-rotation in auditory neglect is also present when an acoustic identification task is used without explicit localization by the subject. Another aim of experiment 2b was to devise a task that circumvents any connotation with the body sagittal. We therefore used a task where subjects do not have to localize an auditory stimulus in relation to their own body sagittal but instead make simple same/different judgments with respect to words heard from different spatial directions (Ziegler, Kerkhoff, Ten Cate, Artinger, & Zierdt, 2001). Here, we assessed whether different head-on-trunk-positions influence the identification of acoustically presented words in the neglected auditory hemispace in a similar way as found in exp. 2a.

5.2.1 Methods

5.2.1.1 Subjects

Five right-brain lesioned patients with left sided visual neglect due to a single, right hemispheric vascular lesion (Table 5.4), four control patients with a single right-hemispheric vascular lesion but without visual neglect (see Table 5.5), and six age-matched normal subjects (2 f, 4 m; median age: 63, range: 46-70) were tested. None of the subjects had participated in experiment 2a. All subjects had normal hearing sensitivity according to pure-tone audiometry as measured in experiment 2a (data not shown). The three subject groups did not differ according to age (Kruskal-Wallis-Test, Chi-square=1.229, df=2, P > 0.05) and the two patient groups did not differ in their time since lesion (Mann-Whitney-test; Z=-.548, P>0.05). Three patients in either patient group were hemianopic and showed a comparable visual field sparing according to perimetric testing (2-5°).

Table 5.4: Clinical and demographic data of right brain damaged patients of experiment 2b with leftsided visual neglect (NE 1-5). All screening tests used in experiment 2a, except copying, were also performed in experiment 2b. Abbreviations: f: female, m: male; R: right, L: left; TSL: Time since lesion; ICB: intracerebral bleeding; MCI: middle cerebral artery infarction; par, temp, front: parietal, temporal, frontal; HH: Homonymous hemianopia; Bisection: the deviation from the true midline is given (in mm); Cancell.: cancellation of 30 numbers embedded in 200 distractors: L/R: the number of left/right sided omissions is given. Reading errors: text of 180 words, errors are displayed (normal cutoff: max. 2 errors). Md: Median

Code	Age Sex	Etiology, TSL	Lesion Side, Localization	Field Defect/ Sparing (°)	Bisection	Cancell. L/R	Reading Errors
NE1	65,m	MCI, 2	R-front-temp	HH, 3	+6	10/7	50
NE2	67,m	MCI, 2	R-par-temp	normal	+38	5/2	15
NE3	81,m	MCI, 3	R-par	HH, 5	+13	1/1	15
NE4	72,f	MCI, 3	R-par-temp	HH, 3	+58	10/7	100
NE5	62,m	ICB,2	R-Thal	normal	+2	10/5	122
MEAN	**69.4 yrs Md: 67**	**TSL: 2.4 Md: 3.0**	**---**		**+23.4 mm**	**7.2/4.4**	**60.4**

Table 5.5: Clinical and demographic data of right brain damaged patients of experiment 2b without left sided visual neglect (Right Hemispheric Damage, RHD 6-9). All screening tests used in experiment 2a, except copying, were also performed in experiment 2b. Abbreviations: f: female, m: male; R: right, L: left; TSL: Time since lesion; MCI: middle cerebral artery infarction; PCI: posterior cerebral artery infarction; occ, par, temp: occipital, parietal, temporal; HH: Homonymous hemianopia; Bisection: the deviation from the true midline is given (in mm); Cancell.: cancellation of 30 numbers embedded in 200 distractors: L/R: the number of left/right sided omissions is given. Reading errors: text of 180 words, errors are displayed (normal cutoff: max. 2 errors). Md: Median

Code	Age Sex	Etiology TSL	Lesion Side, Localization	Field Defect/ Sparing (°)	Bisection	Cancell. L/R	Reading Errors
RHD6	71,f	MCI, 3	R-temp-par	HH, 5	-5	1/0	4
RHD7	57,m	MCI, 13	R-temp-par	HH, 2	+1	2/0	5
RHD8	67,m	PCI,2	R-occ	HH, 4	+5	0/0	1
RHD9	62,m	MCI,2	R-temp-par	normal	+4	0/0	1
MEAN	**65.5 yrs Md: 67**	**TSL: 5.0 Md: 3.0**	**---**	**Sparing: 2-5°, Md: 4°**	**+1.3 mm**	**0.8/0.0**	**2.8**

5.2.1.2 *Spatial word identification task*

Subjects were presented pairs of spoken monosyllabic words (interstimulus interval: 1 sec) over an AKG K 240 headphone (Ziegler et al., 2001). They were asked to respond verbally after hearing each word pair indicating “same” or “different” for same/different word pairs, respectively. Half of the pairs were identical (N=48), while the remaining half differed in either the consonantal onset (house - mouse) or their vocalic nucleus (foot - feet). Spoken words were passed through FIR-filters with directional dependent head-related transfer functions to simulate different virtual sound locations in the horizontal plane (Kerkhoff et al., 1999). The sound sources of the two words could either be in a left (-90°, -30°), a central (-30°, +30°), or a right sector (+30°, +90°). Word discrimination error counts (proportion correct) were used as dependent variable. Hence, this task involved no explicit spatial localization of a stimulus but only a decision whether two sequentially heard words were same or different.

5.2.1.3 Experimental conditions

The experimental conditions (head straight, head leftwards rotated by 20°, head rightward rotated by 20 °), as well as the testing room and general experimental setup were identical to those in experiment 2a.

5.2.1.4 Data analysis

Due to the categorical quality of the data (same-different judgments), non-parametric statistics (high loglinear analysis) were performed for numbers of correct responses between all three groups.

Effects of “head position” (left, right, straight) and “stimulation side” (left vs. mid or right) were confined to the neglect group using Chi^2-Tests since both control groups made almost no errors. Interaction between those two factors was computed by using logit-analysis carried out with a custom-model with main effects “head position” and “stimulus side”.

5.2.2 Results

A comparison of the three groups for differences in numbers of correct responses revealed a significantly impaired performance of the neglect patients relative to both the normal controls (chi^2=369, p<.001) and the non-neglecting patients (chi^2=130, p<.001).

In the neglect group, a comparison of correct responses to stimuli from the left versus stimuli from mid or right positions by a chi^2-test revealed a significant main effect of stimulation side ($\chi2 = 42$, $p < .001$; exact, 2-sided), with a marked increase of false responses from right to left.

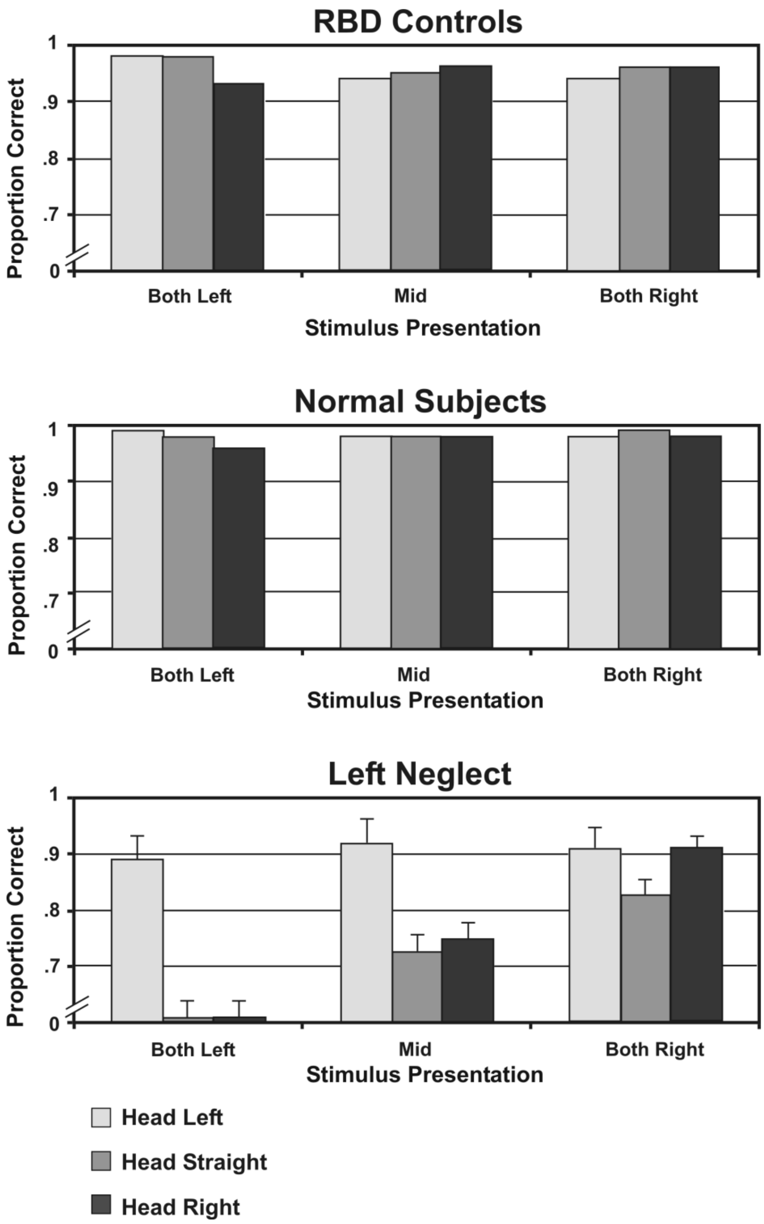

Figure 5.4: Mean proportion correct in the auditory word identification task (experiment 2b) in three subject groups: patients with left neglect (n=5), patients with right brain damage but without neglect (n=4), healthy control subjects (n=6) across the three experimental conditions of head-on-trunk-position (head straight, head left 20°, head right 20°, identical to experiment 2a).

Comparison of correct responses under the head left condition vs. the head central or right condition revealed an equally strong main effect of the head position factor ($\chi 2 = 51$, $p < .001$; exact; 2-sided), hence significantly fewer errors occurred in the head-left condition. To test the interaction between these two factors, a logit-analysis was carried out with a custom-model containing only main effects of head position and stimulus side. The goodness-of-fit-test of this model, which contained no interaction term, was highly significant (Likelihood Ratio = 15 (df=4), $p < .001$), indicating that a significant proportion of the variation in the data remained unexplained relative to a full logit-model. Hence, the interaction seen in Figure 5.4 (bottom) must be considered meaningful. This means that leftward head orientation significantly improved word identification in the contralesional, left space sector and in the central sector, selectively in the neglect patients.

Moreover, the results displayed in Figure 5.4 show that the novel task that we used was sensitive to auditory neglect, since the neglect patients showed a clear gradient of improvement in the discrimination of word pairs presented in the left or mid versus the right space sector. Such spatial performance gradients have typically been reported for *visual* neglect tasks (for review, see Kerkhoff, 2001). No such gradient was obtained in the normal subjects and the right-brain-damaged control patients. Furthermore, it can be seen from the data that there was a clear ceiling effect in the non-neglecting patients and normal subjects, indicating that the task was relatively easy for them.

5.2.3 Discussion

Experiment 2b confirmed the facilitatory effect of leftward head orientation on auditory neglect as obtained in experiment 2a, but in a totally different task focusing on identification instead of spatial localization. Whereas RBD control patients and normal subjects showed a clear ceiling effect in this task (with on average 93-100 % correct in all conditions) the neglect patients showed the typical performance gradient across the contra- and ipsilesional hemispace that has often been found in visual neglect tests (Kerkhoff, 2001).

The results support the findings in experiment 2a and allow the conclusion that leftward head-on-trunk-rotation alleviates neglect related auditory identification deficits in a similar way as in the localization task (experiment 2a.). How can this finding be integrated with the view that acoustic identification tasks are typically viewed as a ventral stream function (Clarke &

Bellmann Thiran, 2004)? There are at least two possible answers to this question. Either, the improvement of word discrimination in left and central space stems directly from increased activation of ventral stream areas (presumably stronger in the left hemisphere) engaged in word identification. This hypothesis seems unlikely given that neurons in dorsal but not ventral stream areas are highly sensitive to eye- and head-position (Duhamel, Bremmer, Benhamed, & Graf, 1997; Andersen, Snyder, Bradley, & Xing, 1997). Alternatively, the improvement originates from the activation of auditory dorsal stream functions by leftward head position in the neglect group. As many neurons in the macaque parietal cortex are modulated by eye- and head-position (see above) it seems more plausible that posterior parietal cortex codes the spatial aspects of a sound image (see also (Weeks et al., 1999) and in this way facilitates word identification in ventral auditory areas (Bellmann Thiran & Clarke, 2003). We therefore assume that improvement in word identification during leftward head rotation in neglect patients results from a better spatial coding of the sound source, presumably in dorsal brain areas. This in turn might enable a better word processing in ventral auditory areas of the left hemisphere. This hypothesis is compatible with views according to which parietal cortex is crucially involved in this type of auditory “streaming” (Carlyon, 2004).

5.3 General discussion Experiment 2

The previous experiments showed clearly that leftward head-on-trunk-rotation selectively improves performance in auditory “where” and “what” tasks in patients with left sided auditory (and visual) neglect. This result is in line with the facilitatory effects of other sensory and cognitive stimulations on visual, tactile, motor and representational neglect previously reported (Vallar et al., 1997; Robertson & Manly, 2002; Rossetti & Rode, 2002). However, despite these numerous studies little is known about the modulation of auditory neglect. Studies in normal subjects indicated that head-on-trunk-position (Lewald & Ehrenstein, 1998), neck-muscle-vibration (Lewald et al., 1999) and vestibular stimulation (Lewald & Karnath, 2001) all modulate auditory lateralization judgments or performance of the left ear in dichotic listening

(Schüeli, Henn, & Brugger, 1999). In general, these effects are significant but relatively small (i.e., 1-1.5 dB or 3-4.5° with eccentric head-rotation or neck muscle vibration (Lewald & Ehrenstein, 1998; Lewald et al., 1999). In comparison to these data the effect of leftward head-on-trunk-rotation seems quite strong in our neglect patients (approximately 25° difference between left-head-orientation versus any of the two other conditions in experiment 2a). Hence, auditory localization in azimuth is strongly affected by head-on-trunk-signals especially in neglect patients. The results of the non-neglecting control patients and normal subjects in general agree with previous studies, showing typically a shift of the ASMP opposite to the direction of head rotation (Lewald & Ehrenstein, 1998). This effect has been interpreted as serving perceptual stability, i.e. keeping the sound image close to the subject despite eccentric head positioning (cf. Lewald & Ehrenstein, 1998; Lackner, 1973).

Interestingly, the effect of leftward head rotation in neglect is not restricted to localization tasks but is also found in a word identification task sensitive to neglect (experiment 2b). As argued above we speculate that this effect results from improved preprocessing of the “spatial” aspect of the sound image in auditory dorsal stream functions which subsequently allows more efficient processing of the words in auditory ventral stream areas.

How could left-sided head-on-trunk-rotation improve auditory localization and identification on a physiological level? One hypothesis is that it improves the allocation of spatial attention towards the contralesional hemispace in the neglect group. Head position thus could serve as a “cue” shifting attention towards the neglected hemispace. Interestingly, Pugh and colleagues (Pugh et al., 1996) found an attention-related increase of neuronal activity induced by selective attention in posterior-parietal cortex of normal subjects while performing an auditory task. These increased activations could in turn improve the functioning of cerebral networks involved in auditory localization (Weeks et al., 1999), which are also located in posterior parietal cortex.

Another, not necessarily incompatible hypothesis is that the head-position-signal activates both vestibular cortex via neck-afferents (Bottini et al., 2001) as well as posterior parietal cortex (Andersen et al., 1997; Stricanne, Andersen, & Mazzoni, 1996), both of which are involved in multisensory spatial integration. This increased activation could in turn “update” or recalibrate the distorted auditory space map in neglect patients. These and recent findings of vestibular (insular) and parietal cortex activations by caloric-vestibular and neck-vibratory stimulation (Bottini et al., 2001) support the hypothesis that audio-spatial deficits show a remarkable behavioral plasticity in patients with spatial neglect. This suggests that the representations of auditory space in the brain of neglect patients change dynamically within a few minutes. The current head position of the patient seems to represent an important “anchor” for this recalibration in spatial neglect.

6 Synopsis

The present dissertation addressed the analysis and comparison of neglect associated, spatial deficits in various sensory modalities, particularly in those modalities which are less often examined in neglect (tactile and auditory).

In the last decade, several studies have increasingly proposed neglect as a *multisensory* phenomenon, which can, but does not necessarily *has to* affect multiple sensory modalities, such as vision audition or touch (Jacobs et al., 2012; Pavani, Ladavas, & Driver, 2003). As already mentioned above, cortical areas involved in multisensory processing, like the posterior parietal (Angelaki, Gu, & Deangelis, 2009; Bolognini, Olgiati, Rossetti, & Maravita, 2010) or superior temporal cortex, the temporo-parietal junction as well as the insular cortex (Karnath & Dieterich, 2006; Bottini et al., 2001), are most frequently damaged in right brain damaged patients with sensory neglect, providing a possible anatomic explanation for these aspects of multimodality in neglect. Andersen et al. (Andersen et al., 1997) reviewed evidence, that the posterior parietal cortex in the monkey is such a core region in representing and computing space in a multisensory way. To achieve this, visual and auditory signals, eye position and velocity, head position as well as vestibular and proprioceptive signals are used to compute a “gain field” mechanism. This mechanism is realized by cells having special receptive fields, which receive a convergence of different signals, whereas one kind of input (e.g. eye position) modulates the sensitivity (or gain) of a neuron to another input (e.g. retinal information). Put differently, the neuronal firing rate on a retinal signal may vary as a function of orbital eye position, while selectivity (e.g. for a specific retinal stimulus position) of that cell is not modified (Salinas & Sejnowski, 2001). Hence, a head-centered reference frame of spatial locations, irrespective of eye and retinal position, may be provided by a population of such cells, each having specific sensitivities for eye position and retinal position, in sense of a "distributed population code" (Andersen et al., 1997).

Several studies indicate that posterior parietal areas may serve similar functions in humans (Bolognini et al., 2010; Nyffeler et al., 2008; Ko, Han, Park, Seo, & Kim, 2008; Lewald, Foltys, & Topper, 2002; Murray & Spierer, 2011), thus probably playing an important role in the understanding, modulation and, finally, also the rehabilitation of multimodal neglect. Similarly, the vestibular, posterior insular cortex (Dieterich & Brandt, 2015; Khan & Chang, 2013; Lopez et al., 2012; Karnath & Dieterich, 2006) is also assumed to play a pivotal role in human multisensory perception and integration, or put differently, in multisensory space representation.

The two experiments reported here may contribute to current research concerning multimodal neglect and the modality-specific characteristics in neglect patients and – probably also in right brain damaged controls without obvious clinical signs of neglect in daily life.

Experiment 1 shed light on the exploratory deficits in visual and tactile search in right brain damaged patients with and without neglect, whereas experiment 2 provided new insights into the auditory lateralization as well as identification performance in patients with auditory neglect and their modulation by head-on-trunk-position. In the following, I will discuss some aspects of these two studies that were not yet addressed in the discussions earlier.

6.1 Suitability of visual neglect screening tests for the assessment of multimodal neglect deficits

All patient subgroups were assigned to right brain damaged groups with and without neglect using standardized visual neglect screening tasks, e.g. line bisection (Schenkenberg et al., 1980) or cancellation tasks (Wilson et al., 1987). They have in common that they provide diagnostic information concerning only the visual modality, irrespective of neglect associated deficits in other modalities. Indeed, both experiments reported here support the assumption of their suitability to detect multimodal sensory neglect, at least as tactile and auditory modalities are concerned. Neglect patients assigned to the neglect subgroup showed clear neglect associated exploration as well as sound localization and identification deficits, which can be interpreted on the basis of a multimodal, contralesional neglect of or deficient spatial localization of sensory stimuli. Furthermore, typical patterns of visual neglect signs were also, at least as a tendency, seen in the tactile and auditory modalities. The well-known left-right lateralization typically observed in acute visual neglect, manifesting itself in a gradient-like pattern of deficits from left to right hemispace, was observable in all three sensory modalities in the present studies. Further research may probably describe this spatial gradient in the tactile modality in greater detail, by evaluating omission and perseveration rates in specific parts (e.g. eccentric positions) of the search board.

6.2 Neuropsychological explanation model for neglect associated deficits

Besides suitability of neglect screening tests, results of the present studies may also be interpreted as evidence for a multimodal space representation as proposed earlier (Karnath, 1994a), providing a possible explanatory basis for neglect associated deficits after brain damage (Karnath & Dieterich, 2006). On the one hand, our data suggest multisensory deficits affecting multiple modular sensory systems in a similar way, namely left sided disregard of stimuli as well as a pathologically rightward attention orientation. In auditory neglect, the latter fact was clinically observable by a lack of any modulating effect of rightward head rotation in neglect patients, while repeated search in the visual and tactile exploration task was rather shown on the right side of the search table. On the other hand, the ameliorating effect of head rotation on auditory lateralization and identification is also well interpretable within the framework of an egocentric and multimodal spatial reference frame. The effect of head rotation may unfold its ameliorating effect by highlighting leftward stimuli due to rotation of the head to the left, but it may also be understood as an enrichment of neck-proprioceptive sensory information induced by lengthening the neck trapezium muscles as it is seen in neck-muscle vibration. In case of experiment 1, no significant effect of GVS was found, probably due to the small and heterogeneous patient samples. Here, further research is needed to evaluate the potential therapeutic effect of GVS on rather difficult exploration tasks involving a large area of near and far peripersonal space spanning almost 180° around the subjects' body.

6.3 Exploration deficits in right brain damaged patients without overt spatial neglect: Omissions and perseverations as independent parameters of multimodal search

As shown in the appropriate results section of experiment 1, not only neglect patients showed spatial exploration deficits in the visual and tactile search tasks. Although to a smaller extent, (see experiment 1), also right brain damaged patients *without* neglect according the conventional screening tests did suffer - at least partially - from a residual deficit in exploration. In Experiment 1, right brain damaged control patients predominantly showed an exploration performance regarding omissions which, in fact, was quantitatively *better* than that of neglect patients but worse than that of healthy normal controls. This exploration deficit did not entail a consistent, spatial lateralization bias, as in the neglect group. Rather, they tended to repeat their search behavior repetitively. Right brain damaged patients with and without neglect thus showed measurable impairments in explorative behavior, especially in the visual task. While healthy controls showed only small numbers of repetitions in both hemifields, hence showed a ceiling effect in the visual exploration task, both patient subgroups showed overall higher perseveration rates (as an index of repetitive search). Put differently: both patient groups showed this pathological revisiting search pattern, but differed in the lateralization bias already mentioned above, which was present in the neglect patients but not in the right brain damaged controls. This result, which also has to be interpreted as a tendency, replicates previous research (Nys, van Zandvoort, van der Worp, Kappelle, & De Haan, 2006) and can be seen as another impairment in space representation in right brain damaged patients without neglect, even if modality specific task difficulty is low (or even lower). This result is in line with previous research (Ronchi et al., 2009; Ronchi et al., 2012; Rusconi et al., 2002; Pia et al., 2009; Vallar, Zilli, Gandola, & Bottini, 2006), suggesting perseveration and omission behavior in neglect patients as two independent exploration deficits, caused by different pathological mechanisms. According to this view, repeated search in neglect patients may be explained by two possible hypotheses: namely a) allochiria, assumed as a perceptual displacement of stimuli from the contralesional to the ipsilesional side (Halligan, Marshall, & Wade, 1992) and/or b) directional hypokinesia, which explains repetitive search behavior in the right hemifield due to left sided stimuli which are perceived to be out of reach but should still be cancelled (Heilman et al., 1985). Both accounts assume a kind of unconscious, competitive effect of stimuli in the neglected, left hemispace on the (repetitive) search behavior in right hemispace. Evidence for both accounts is found in the recent literature (Manly, Woldt, Watson, & Warburton, 2002; Bottini & Toraldo, 2003; Pia et al., 2009; Vallar et al., 2006; Toraldo et al., 2005; Rusconi et al., 2002; Nys et al., 2006).

The present findings are in line with both of these assumptions, and hopefully may inspire further research to analyze these phenomena in right brain damaged patients without neglect in greater detail. As proposed by Rusconi and colleagues (Rusconi et al., 2002), the overt visuo-spatial neglect may only play a “triggering role” in the disordered spatial search behavior observed after right brain damage. Neuroanatomical data may further help to clarify the role of frontal and / or subcortical structures, e.g. basal ganglia (Rusconi et al., 2002; Vallar et al., 2006; Damasio, Damasio, & Chang Chui, 1980) in this context.

6.4 Cross-modal therapeutic effects on sensory neglect

Last but not least, the present study also addressed cross-modal effects of sensory neglect.

Whereas no clear conclusion can be drawn regarding galvanic vestibular stimulation due to the limitations of the exploratory study, neck-proprioceptive stimulation induced by passive head rotation in experiment 2 provides additional evidence for cross-modal therapeutic effects of bottom-up, sensory stimulation techniques on auditory spatial neglect. In line with the explanation model of Karnath mentioned above (Karnath, 1994a), the ameliorating effect of neck-proprioceptive stimulation may be caused by modulating sensory inputs integrated in a multisensory space representation, which is impaired in neglect patients, leading to a lateralization bias as it is described above. Therefore, the ameliorating effect of sensory stimulation may be caused by changing the "weight" of neck-proprioceptive sensory information in this disturbed reference frame, correcting the neglect associated lateralization bias in sense of a reduction of contralesional omissions (Karnath, 1994a; Kerkhoff, 2003).

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