Galvanic-vestibular stimulation influences *multiple* components of visual neglect

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Abstract: Neglect patients show contralesional deficits in egocentric and object-centred visuospatial tasks which may dissociate. The extent to which these different phenomena are modulated by sensory stimulation remains to be clarified. Galvanic Vestibular Stimulation (GVS) induces polarity-specific changes in the cortical vestibular systems which are known to be related to the syndrome of spatial neglect. Subliminal GVS induces imperceptible, vestibular stimulation without the unpleasant side effects (nystagmus, vertigo) induced by caloric vestibular stimulation. While previous studies showed vestibular stimulation effects on egocentric spatial neglect phenomena, such effects were rarely demonstrated in object-centred neglect. Here, we applied bipolar subsensory GVS over the mastoids (mean intensity: 0.7 mA) to investigate its influence on egocentric (digit cancellation, text copying), object-centred (copy of symmetrical figures), or both (line bisection) components of visual neglect in 24 patients with unilateral right hemisphere stroke. Patients were assigned to two patient groups (impaired vs. normal in the respective task) on the basis of cut-off scores derived from the literature or from normal controls. Both groups performed these tasks under three experimental conditions: a) sham-baseline GVS where no electric current was applied, b) left cathodal GVS and c) right cathodal GVS, for a period of 20 minutes per session. Left-cathodal GVS significantly improved line bisection and text copying whereas right-cathodal GVS significantly ameliorated figure copying and digit cancellation. These GVS effects were selectively observed in the impaired - but not in the unimpaired patient group. In conclusion, subliminal GVS modulates ego-*and* object-centred components of visual neglect in a polarity-specific way.

Key words: egocentric– object-centred – neglect - attention – rehabilitation - galvanic vestibular stimulation

1. Introduction

Neglect is a multicomponent syndrome where patients typically fail to explore sensory stimuli in the contralesional hemispace or body side. Neglect most often follows after right-hemispheric lesions (Kerkhoff, 2001) and entails several different components (Grimsen, Hildebrandt, & Fahle, 2008). For example, neglect patients may show severe impairments in a wide range of egocentric tests of neglect including cancellation, visual and tactile exploration as well as writing. These *egocentric* neglect phenomena can be defined as a failure to attend to contralateral stimuli in space in relation to one's body midsaggital plane. Hence, the body serves as the egocentric anchor or reference (Ventre & Flandrin, 1984) for the patient´s performance in space. Another component of neglect is termed object-centred neglect. Here, the contralateral side of a single perceptual object is neglected irrespective of its location relative to the viewer. In contrast to egocentric neglect phenomena, the midline of the object and not the patient´s body serves as a reference for tasks like copying a flower or a clock face (Halligan, Fink, Marshall, & Vallar, 2003). Finally, some tests may require a combination of both reference frames. In those tests, the contralateral side of a single perceptual object is neglected but the spatial location of the stimulus relative to the viewer determines the severity of neglect. Horizontal line bisection, for example, may be considered an object-centred task given that the bisection error (LBE) correlates with the extent of the neglected letter string of single words in neglect dyslexia (Reinhart, Wagner, Schulz, Keller, & Kerkhoff, 2013), and covaries with line length (Halligan & Marshall, 1991). On the other hand, LBE has also been found to vary relative to the viewer (Utz, Keller, Kardinal, & Kerkhoff, 2011, i.e. in the Schenkenberg test) and to correlate positively with search- and reading biases in cancellation tasks as well as paragraph reading (Reinhart et al., 2013).

On a neural level, ego- and object-centred visual processing seem to recruit different brain structures (Olson & Gettner, 1996): Single-cell recordings in monkeys have identified neurons in the frontal cortex (Olson & Gettner, 1995) that discharge selectively when the allocation of attention to the contralateral part of a perceptual object is required. This contrasts with the properties of neurons in monkey parietal cortex, where neurons discharge when the allocation of attention to regions in contralateral space is required (Gottlieb, 2002). Functional imaging studies in healthy humans yielded similar findings of differential activations associated with ego- and object-centred space processing (Honda, Wise, Weeks, Deiber, & Hallett, 1999; Vallar et al., 1999): Object-centred visual processing was found to be mostly related to activations in the temporal and - to a smaller extent - in the frontal cortex. Egocentric visual processing, on the other hand, has been associated with activations in the parietal and - to a lesser degree - in the frontal cortex (Vallar et al., 1999). Finally, studies in neuropsychological patients show a similar picture: Hillis et al. (2005) observed object-centred visual neglect phenomena in a cancellation task in patients with lesions of the right superior temporal gyrus, but egocentric errors (omissions) in the same task in patients with damage of the right angular gyrus. Put differently: egocentric visual neglect phenomena are mostly linked to the dorsal visual stream (parieto-frontal cortices) while object-centred visual neglect phenomena are associated with more ventral brain lesions in the temporal lobe (Grimsen et al., 2008; Ptak & Valenza, 2005).

Electrical stimulation of the vestibular system can be induced by placing one electrode behind each ear over the left and right mastoid respectively (termed galvanic vestibular stimulation or GVS, for review see Utz, Dimova, Oppenländer, & Kerkhoff, 2010). Underneath the mastoids the vestibular nerve projects from the inner ear to the vestibular brain stem nuclei, which in turn are interconnected with the nucleus ventroposterolateralis of the thalamus. From there, ascending vestibular fiber pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a, b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC). Although there is no primary vestibular cortex as in the visual, auditory or tactile modality, the above mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC (Guldin & Grusser, 1998). Practically, GVS consists of applying direct current to the mastoids – usually delivered by a small battery-driven constant current stimulator (Wilkinson, Nicholls, Pattenden, Kilduff, & Milberg, 2008). Subliminal GVS can be administered by adjusting the current intensity below an individual's sensory threshold. This has the methodological advantage that different GVS protocols and polarities can be manipulated elegantly without the patient´s knowledge that might otherwise influence his performance due to "spatial cueing" effects induced by a tingling sensation under one electrode. Furthermore, GVS is painless, easily applicable, safe, and induces minimal side effects when used in accordance with standard safety guidelines (Utz et al., 2011).

GVS has significant effects on a wide variety of cognitive and perceptual tasks, both in healthy subjects and neurological patients (for review see Utz et al., 2010). For example, Wilkinson and coworkers found that GVS facilitated visual memory recall in healthy subjects (Wilkinson et al., 2008) and improved visuo-constructive deficits in a right-hemisphere lesioned patient (Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010). A recent study by Wilkinson, Ferguson, & Worley (2012) found significant effects of GVS on the electrophysiological component (N170) in a face processing task. This underlines the physiological effects of GVS in modulating neuronal activity in visual areas of the ventral stream. Moreover, a few sessions of GVS were shown to induce a lasting treatment effect in visuospatial neglect (Wilkinson, Zubko, Sakel, Coulton, Higgins, & Pullicino, 2014). Furthermore, Saj, Honore, & Rousseaux (2006) demonstrated a positive effect of left-cathodal GVS on the perceptual tilt of the subjective vertical in right-hemisphere lesioned patients with left neglect. Furthermore, Kerkhoff et al. (2011) and Schmidt et al. (2013b) found a long-lasting beneficial effect after a few sessions of left- and right-cathodal GVS in tactile extinction. Finally, Utz et al. (2011) showed a significant improvement in line bisection (Schenkenberg test) after right- and partially also after left-cathodal GVS in 6 patients with left visuospatial neglect, but no effect in 11 right-hemisphere stroke patients without neglect.

In summary, there is increasing evidence that GVS can significantly modulate a range of cognitive capacities or impairments in both healthy subjects and neurological patients (partially with neglect). So far, it is not known however whether the modulatory effect of GVS on neglect is restricted to egocentric space processing such as observed cancellation tasks (Rorsman, Magnusson, & Johansson, 1999) or whether it has also the capacity to influence additional components of impaired space processing such as object-centred neglect. As the brain areas associated with object-centred visual attention (Honda et al., 1999) are remote from those typically activated by GVS (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001) it is unclear whether their activity can be modulated by GVS. Both, from a theoretical and a clinical viewpoint, it would be interesting to know whether galvanic vestibular stimulation modulates not only egocentric but also object-centred components of visual neglect. Clinically, this is clearly relevant as neglect patients are typically impaired in both spatial components of visual neglect and require therefore specific rehabilitation techniques for intervention. Moreover, while egocentric neglect phenomena can be treated by a variety of novel therapies (for review see Kerkhoff & Schenk, 2012) no treatment is currently available for object-centred neglect, to the best of our knowledge. Theoretically, a potential vestibular influence on these different components is also interesting, as it may clarify the relationship between mechanisms of visual attention operating in ego- vs. object centred coordinate systems and the cortical vestibular system (Grimsen et al., 2008; Olson & Gettner, 1996). Hence, the aim of the present study was to investigate whether subliminal GVS modulates *multiple* (ego-, object-centred) spatial processing components of visual neglect, and whether these effects are polarity-specific.

2. Patients and Methods

2.1. Patients and healthy control subjects

The study - which was approved by the local ethics committee (Ärztekammer des Saarlandes, Nr. 147/08, 16.9.2008) - included 24 patients with unilateral right-sided stroke (Table 1). Inclusion criteria were right-handedness and a single right hemisphere infarction or haemorrhage. Exclusion criteria were other neurological or psychiatric diseases, epilepsy, a sensitive scalp skin, metallic brain implants and medications altering the level of cortical excitability (Iyer et al., 2005). The participants were 10 women and 14 men with a median age of 63.6 years (range 42-84 years), and a median time since lesion of 2 months (range: 1-84 months). For each of the four neglect tasks described below the patients were – depending on their performance in the sham-baseline condition - allocated to a patient group *with neglect* (RBD+) in the specific task or a patient group *without neglect* (RBD-) in the respective task.

In addition, 28 healthy, age-matched control subjects (11 male, 17 female, median age: 56 years (range: 44-75 years) were tested to collect normative data for these tasks. This was achieved by establishing cut-off criteria for assigning patients to the RBD- or RBD+ groups. The healthy control subjects did not participate in the experimental (stimulation) sessions.

Table 1 about here

2.2 Experimental procedures

In the first session all participants performed the four tasks while the electrodes of the stimulation device were fixed over the mastoids but not active (Sham=Baseline condition). To this purpose, after fixing the electrodes, the current was initially turned on until the subject perceived a tingling sensation, after which the current was smoothly turned off within 30 seconds, without the patient being aware of this (due to the subthreshold stimulation, see below). The stimulator was always invisible for the subject. This created an effective sham-stimulation since the subjects could not discriminate between the conditions where real current was applied and those where the current was turned off due to the imperceptible, sub-threshold intensity of the stimulus. In sessions 2 and 3, the patients repeated all experimental tasks, but received subliminal GVS (either left-cathodal/right-anodal or left-anodal/right-cathodal GVS). The sequence of these 2 experimental conditions was counterbalanced within each group, with one half of the participants receiving left-cathodal/right-anodal GVS in session 2 and right-cathodal/left-anodal GVS in session 3, and the other half receiving the opposite sequence. The three sessions were performed on three separate days. The total experiment was completed within 5 days. Each complete session lasted approximately one hour. GVS-stimulation started a few seconds before the task instruction by the experimenter and terminated immediately after completion of the four tests. All four tests were completed within 20 minutes in every session.

Galvanic bipolar stimulation was delivered by a constant direct current (DC) stimulator (9 voltage battery, Type: ED 2011, manufacturer: DKI GmbH, DE-01277 Dresden). The carbon-rubber electrodes (50 mm × 35 mm) were fastened on the skin over each mastoid (binaural stimulation), in order to activate the peripheral vestibular organs. The conditions were termed Cathode Left (CL) when the cathode was placed over the left mastoid and the anode on the right, and Cathode Right (CR) when polarization was inversed. Similar to Rorsman et al. (1999) we stimulated below the sensation threshold (subliminal) in order to prevent awareness of any electrical stimulation in the 3 experimental conditions. A switch on the stimulation device delivered current at individually adjusted levels for each patient. This threshold was individually determined in the Sham/Baseline condition by slowly increasing current intensity in steps of 0.1 mA until the subject indicated a tingling sensation. The current was subsequently reduced until the subject reported that the sensation had disappeared. This procedure was repeated a second time and the median of these 4 threshold values was defined as the sensory threshold. This value of current intensity was then used for the CL and CR sessions. The mean threshold level across all patients was 0.7 mA (range: 0.4-1.5 mA). This strategy of subliminal GVS eliminates any “spatial cueing” effects as a consequence of the tingling sensation typically felt by the subject when *above-threshold* electrical current is delivered to the anode on the mastoid.

2.3 Experimental neglect tests

Number cancellation

Cancellation tasks are classic tools for assessing egocentric visual neglect and considered most sensitive for its diagnosis (Machner, Mah, Gorgoraptis, & Husain, 2012). Here, patients were presented with a 29.7 x 21 cm white sheet of paper containing 200 randomly distributed single digit numbers ranging from 0 to 9 (cf. Reinhart, Schindler, & Kerkhoff, 2011). Every number was present 20 times on the display, 10 times on the left side and 10 times on the right side (Fig. 1). Following a demonstration in which the examiner crossed out one of these digits on the right side of the paper on a sample sheet (which was not scored), the patients were asked to cross out all target digits (i.e. all “7”) on a separate test sheet. Patients were required to search for different target digits (with different spatial positions of the target stimuli in each subtest) in each experimental session to eliminate memory or practice effects. None of the test sheets was given twice to the same patient and the order of target type was randomised across subjects.

The mere number of neglected targets in a cancellation task might not be a sensitive measure for the severity of egocentric neglect as it provides no information about the degree of contralesional bias in the distribution of omissions. Therefore, the centre of cancellation (CoC) was calculated as a measure of spatial bias based on the procedure described in Binder, Marshall, Lazar, Benjamin, & Mohr (1992) and Rorden & Karnath (2010). The CoC accounts for the spatial position of every omitted target which has the advantage of measuring neglect severity as a function of the search bias on a continuous scale (Rorden & Karnath 2010). CoC scores can vary between -1 and +1 with values close to +1 indicating a severe rightward neglect in a patient who only cancelled the rightmost targets (and vice versa for a score of -1). Accordingly, search performances that show a large number of *evenly* distributed omissions result in CoC values close to zero. A patient was assigned to the RBD+ group when the CoC was smaller than 0.100 (including negative scores). The available norms (from the 28 healthy control subjects) for the number cancellation test show detection rates of 100% for left-sided target stimuli in healthy controls and even in RBD patients without spatial neglect (Reinhart et al., 2011). The suggested cut-offs for the spatial cancellation biases (CoC) derived from the Bells Test and the Letter Cancellation Test in Rorden & Karnath's (2010) study were 0.081 and 0.083. Therefore, our criteria can be considered as conservative. We chose these conservative criteria to avoid ceiling effects in the RBD- group. The assignments to the RBD+ group compliant with both criteria were identical ($r = 1.0$, $p < 0.001$).

Figure 1 about here (neglect tests)

Copy of Symmetrical Figures

Object-centred visual neglect was assessed by copying symmetrical figures (Fig. 1). Six different figures (two for each session) were drawn by the patients using their ipsilesional, right hand. None of the drawings was given twice to the same patient to rule out practice or memory effects. The drawing was placed in the centre of an A4 (29.7 x 21.0 cm) sheet of paper and the patient was asked to copy the figure below the template under a horizontal line (see figure 1). For each of the three conditions (Sham, CL, CR) omissions (missing details of the reproduced figure) were counted. As the available norms (from the 28 healthy control subjects) showed no left- or right-sided omissions in figure copying, the cut-off value for the assignment to the RBD+ versus RBD- group was set at 0 omissions. Patients who showed at least 1 omission on the left side in the Baseline/Sham-condition were assigned to the RBD+ group, all others were assigned to the RBD- group.

Horizontal line bisection

We used the horizontal line-bisection subtest from the German version of the BIT (Wilson, Cockburn, & Halligan, 1987) in order to detect the degree and direction of the combination of egocentric and object centred aspects of visual neglect. Three horizontal lines (length: 200 x 1 mm) were presented on a 29.4 x 21 cm paper sheet (landscape format, see also Fig. 1). Subjects were instructed to mark the middle of each line using their right hand and a pencil. For each of the three conditions (Sham, CL, CR) the mean deviation from the objective centre of the three lines was measured and averaged in mm. Studies in normal subjects have shown a maximum deviation of +4.51 mm to the right side in this line bisection test, which was taken as the cut-off value for spatial neglect (Fels & Geissner, 1997). Thus, patients with a mean rightward deviation beyond +4.51 mm in the Sham condition were assigned to the RBD+ group whereas all others were assigned to the RBD-group.

Text copying

Text copying was assessed by asking patients to copy a short text directly (Arial, 44 pt, right-aligned). Interestingly, writing has received little attention in neglect research while reading and neglect dyslexia have been studied quite often in the last years (Reinhart, Keller, & Kerkhoff, 2010). Undoubtedly, both are relevant for daily life. Analogous to paragraph reading tasks where omissions of whole words on the contralesional side indicate egocentric deficits while substitutions or misreading of contralesional parts of single words reflect a word- or object-centred neglect deficit (Reinhart et al., 2011; Reinhart, Keller, & Kerkhoff, 2010) we defined two types of errors in text copying: Space-related omissions of whole words on the left side were classified as egocentric deficits while omissions or miswritings of left-sided parts (syllables, letters) of single words were considered manifestations of object- (word) centred neglect. Hence, the text copy task entailed both egocentric and object-centred components which were analysed separately.

Six different sentences (two for each experimental session), arranged centrally in three lines on a 29.7 x 21 cm white sheet of paper, were taken from a German fairy tale book (Fig. 1). None of the sentences were given twice to the same patient to rule out repetition or memory effects. This stimulus sheet was presented in front of the patient and aligned with the body midsaggital plane. The patient was instructed to write down the text on an empty sheet of paper as correctly as possible. Omissions of letters and words were counted separately for each session. As available norms showed no omissions in this task, the cut-off value for assignment of patients into the two groups (RBD+, RBD-) was 0. Patients who showed at least 1 omission in the Sham condition were assigned to the RBD+ group, all others were assigned to the RBD- group.

2.4. Statistics

ANOVAs were carried out for the parametric data of the cancellation (CoC) and the line bisection tasks (LBE in mm). The results of the ANOVAs were Greenhouse-Geisser corrected when sphericity was violated according to significant Mauchley-Tests. As the visual extent of the words used in the text copying tasks as well as the visual extent of details of the figures used in the figure copy tasks was highly variable, we classified the number of omitted words and of omitted figure details as nonparametric, not interval scaled variables. Therefore, nonparametric statistics (Friedman-Tests, Wilcoxon-Tests) were computed for these two tests. The alpha-level of subsequent analyses was Bonferroni-adjusted according to Holm´s method (Holm, 1979).

3. Results

3.1. *Spatial bias in number cancellation*

All 24 patients performed this task. Eleven patients were assigned to the RBD+ group and 13 to the RBD- group according to the criteria described above (section 2.3). A 2×3 ANOVA with the factors group (RBD+ and RBD-) and stimulation condition (sham, left GVS, and right GVS) revealed significant main effects of stimulation condition [$F(1.35, 29.71) = 5.99$, $p = 0.013$] and group [$F(1, 22) = 47.88$, $p < 0.001$] and a significant stimulation condition × group interaction [$F(1.35, 27.71) = 6.73$, $p = 0.009$]. Subsequent t-tests revealed a significant reduction of the CoC during CR compared to sham stimulation [mean difference = 0.164, $t(10) = 3.61$, $p = 0.005$] in the RBD+ group. There were no significant differences between CL and sham or CL and CR stimulation (all ps > 0.070). For the RBD- group, subsequent t-test were significant for the comparisons between sham and CL [$t(12)= -2.87$, $p = 0.014$] and CL vs. CR stimulation [$t(12)= -2.75$, $p = 0.017$], both indicating an *increased* CoC in the CL condition. However, it should be noted that the mean CoC during CL (CoC = 0.041) was below the cut off of 0.100. There was no significant difference between sham and CR stimulation [$t(12)= -0.05$, $p = 0.96$]. The results are shown in Figure 2.

Figure 2 about here

3.2. Copy of symmetrical figures

21 out of 24 patients completed this task. Three patients were unable to complete this task due to fatigue. In the RBD+ group (N=14) Friedman analyses of variance showed a significant GVS effect across the experimental sessions (X^2 = 11.65, df = 2, p = 0.003). Subsequent Wilcoxon tests revealed neither significant differences between CL and Sham (Z = -1.84, p = 0.070, n.s.) nor between CL and CR (Z = -1.31, p = 0.190, n.s.). There was, however, a significant decrease of omissions in the CR condition as compared to Sham (Z = -2.46, p = 0.014). No significant effects were found in the RBD- group across the experimental sessions (N=7; Friedman-test, X^2 = 2.00, df = 2, p = 0.368, n.s.; Fig. 2).

3.3. Horizontal line bisection

23 out of 24 patients completed this task. One patient misunderstood the instruction and was therefore excluded. Twelve patients were assigned to the RBD+ group and 11 to the RBD- group according to the criteria described above (section 2.3). A 2×3 ANOVA with the factors group (RBD+ and RBD-) and stimulation condition (sham, left GVS, and right GVS) revealed significant effects of stimulation condition [F(2, 42) = 4.52 p = 0.017] and group [F(1, 21) = 19.14, p < 0.001] and a significant stimulation condition × group interaction [F(2, 42) = 5.81, p = 0.006]. Subsequent t-tests yielded a significant reduction of the LBE during CL compared to sham stimulation [mean difference = 14 mm, t(11) = 4.00, p = 0.002] in the RBD+ group. There were no significant differences between CR and sham or CL and CR stimulation (all ps > 0.08). Furthermore, there were no significant differences in the RBD- group (all ps > 0.29; Fig. 2).

3.4. Text copying

21 out of 24 patients completed this task. Omissions of whole words on the left

side in copying accounted for 99% of errors while word-centred copying errors were very rare (1 % of all errors). Therefore, only left-sided omission errors were analysed. In the RBD+ group (N=12) Friedman analyses of variance showed a significant effect of GVS (X^2 = 9.39, df = 2, p = 0.009). Significant differences were found neither between CR and Sham (Z = -1.50, p = 0.133, n.s.) nor between the conditions CR and CL (Z = -1.71, p = 0.088, n.s.). There was a significant decrease of omissions in the patients´ copy in the CL condition as compared to Sham (Z = -2.84, p = 0.004). In contrast, no significant effect of GVS was seen in the RBD- group (N=9, X^2 =2.00, df = 2, p = 0.368, n.s., Fig. 3).

Figure 3 about here

4. Discussion

Several findings are apparent from our study:

1) GVS modulated all components of visual neglect in the RBD+ but not the RBD- group: egocentric, object-centred, and the combination of both aspects. This shows, that GVS affects not only egocentric attentional mechanisms –which could be expected because the vestibular system codes spatial information mainly in an egocentric way (Fitzpatrick & Day, 2004), as well as pure object-centred (symmetrical figure copy) attentional mechanisms but also attention processes that rely on a combination of egocentric and object centred reference systems (line bisection).
2) The effects of GVS were polarity-specific for the different tasks: left-cathodal stimulation improved significantly horizontal line bisection and text copying, while right-cathodal stimulation improved figure copying and number cancellation.

We will discuss these aspects below.

4.1. Effects of GVS on different components of visual neglect

Rorsman et al. (1999) were the first to explore the effects of subliminal, galvanic

GVS on visual neglect using a cancellation test. In line with their pioneering results we found improved contralesional target detection as indicated by a decreased rightward bias (CoC) in the number cancellation task in the RBD+ group. The significant although modest shift of line bisection performance in the RBD- group during CR parallels similar performance deteriorations of the position sense during right-cathodal GVS in healthy subjects (Schmidt et al., 2013). This may be explained by an overexcitation of the vestibular system normally involved in this task in unimpaired (control) patients or in healthy control subjects. Put differently: only patients with a spatial deficit in the task under study may benefit from GVS induced activation.

Also similar to Rorsman et al. (1999) we found a strong effect of left-cathodal GVS on horizontal line bisection. Left-cathodal GVS transiently completely normalized the pathological right-sided bias during line bisection in our neglect group (Fig. 3, upper). In contrast, GVS had no modulating effect in patients showing a leftward line bisection bias (i.e. due to left sided visual field defects). Our results are largely in line with the findings of a recent study by Utz et al.(2011), who found *both* right-cathodal and left-cathodal GVS effective in reducing the rightward bisection bias, with right-cathodal stimulation being slightly but not significantly more potent than left-cathodal stimulation. The bisection task in that study (a modified Schenkenberg test with 27 lines to be bisected; Schenkenberg, Bradford, & Ajax, 1980), however differed from ours (the German version of the BIT with only 3 horizontal lines to be bisected, cf Fig. 1A, (Wilson et al., 1987). Moreover, GVS was applied at 1.5 mA by Utz et al. (2011) instead of subliminal GVS (0.7 mA) in the present study. These task- and stimulation differences may explain the slightly different polarity effects of GVS on line bisection. One plausible hypothesis that could account for the modulating effect of GVS on horizontal line bisection is that GVS decreases the rightward line bisection error selectively in neglect patients by activating preserved structures of the right posterior parietal cortex, which are usually involved in horizontal line bisection performance (Mort et al., 2003; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Interestingly, 6 of our RBD+ patients that were impaired in the line bisection task showed sparing of the right parietal cortex (Tab. 1). Imaging studies of GVS in healthy subjects show widespread cortical activations in the following brain regions: the temporo-parietal junction, the central sulcus, the intraparietal sulcus (Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998), anterior parts of the insula, the thalamus, the putamen, the inferior parietal lobule [Brodmann area (BA) 40], the precentral gyrus (frontal eye field, BA 6), the middle frontal gyrus (prefrontal cortex, BA 46/9), the middle temporal gyrus (BA 37), the superior temporal gyrus (BA 22), and the anterior cingulate gyrus (BA 32) as well as in both cerebellar hemispheres (Bense et al., 2001). This widely activated network related to GVS surrounds and includes the critical lesion locus for impaired line bisection in neglect patients, namely the right angular gyrus (Mort et al, 2003, Verdon et al, 2012). It is therefore conceivable that such activations in neglect patients may have led to the improvement observed here. Finally, Fink et al. (2003) found an effect of suprathreshold GVS on horizontal line bisection in healthy subjects mediated by right parietal activations as assessed with fMRI.

With respect to text copying we found a significant reduction of left-sided omissions under left-cathodal GVS as well as a numerical, but non-significant reduction of such errors after right-cathodal GVS (Fig. 3B). From a behavioural perspective, it is tempting to argue that left-cathodal GVS shifted attention further to the neglected side (as in line bisection, Fig. 3A) thereby leading to a reduction of omissions in text copying. On the neural level, left-cathodal GVS is known to induce bilateral activations of the cortical vestibular system (Fink et al., 2003). These rather symmetrical activations in both cerebral hemispheres might act on two mechanisms related to text copying: exploring further toward the left side of the display and moving the right arm further to the left during copying of the sentences.

Finally, we found – to our knowledge for the first time – a clear effect of vestibular stimulation (GVS) on object-centred neglect in the symmetrical figure copy tasks. This type of task represents in our view a rather pure object-centred task. According to Olson & Gettner (1996) spatial attention is important for the processing of visuospatial information *within* a perceptual object. Here, both GVS conditions reduced the number of contralesional (left) omissions, but only the right-cathodal condition reached significance (Fig. 2B). One plausible explanation is that right-cathodal GVS increased activations in brain areas related to object-centred visual attention, i.e. in the frontal cortex and the ventral visual stream. In fact, imaging studies in healthy subjects showed activations in the precentral gyrus (frontal eye field, BA 6), the middle frontal gyrus (prefrontal cortex, BA 46/9), the middle temporal gyrus (BA 37) and the superior temporal gyrus (BA 22), among others (Bense et al., 2001). GVS, therefore, might lead to an up-regulation of these frontal and ventral stream areas to symmetrical object features as required by the symmetrical figures task in our study. An alternative but not necessarily exclusive hypothesis, is that right-cathodal GVS - which mainly activates the right-hemispheric vestibular system, and temporo-parietal cortex in particular (Fink et al., 2003), leads to a general facilitation of spatially non-lateralized attentional mechanisms within the right fronto-parietal cortex (Husain & Rorden, 2003). This in turn could improve alertness which might result in a more symmetrical performance in copying symmetrical figures. Future studies might investigate the influence of GVS on alertness and object-centred attention in greater detail. Independently of the precise underlying mechanism, our findings may have clinical implications as there is currently no effective treatment available for object-centred visual neglect (Kerkhoff & Schenk, 2012). Our results suggest that GVS might be an interesting candidate for the modulation and even treatment of such deficits in drawing, reading (word-based errors) or related visual pattern tasks which require allocation of attention *within* a structured visual display (Grimsen et al., 2008).

4.2. Polarity-specific effects of GVS

Functional imaging studies have established an unexpected hemispheric asymmetry in the human vestibular system: the right-hemispheric vestibular system is dominantly organised as compared to the left-hemispheric vestibular system (Bartenstein et al., 1998). As a consequence, vestibular stimulation of the right hemisphere – via cathodal galvanic stimulation of the left mastoid (CL) – leads to a stronger and bi-hemispheric activation of the vestibular cortices as well as regions within the adjacent temporo-parietal cortex. In contrast, right-cathodal (CR) stimulation of the right mastoid produces weaker activations restricted to the left vestibular cortex and adjacent temporo-parietal regions. In accordance with these findings, it is interesting to note that we often found that one specific stimulation condition (CL or CR) produced significant reductions in a particular task, while the other condition led to a similar, though weaker, more variable and therefore often non-significant improvement in the same task (cf. Fig. 2,3). While we referred to the asymmetry of cortical vestibular activations after left- versus right-cathodal GVS already in the preceding paragraph as a potential explanation of these polarity effects, other explanations might be plausible as well. For example, the efficacy of left- or right cathodal GVS in modulating performance in a cognitive task might also depend on a certain "activation threshold" that has to be exceeded in order to induce behaviourally observable effects in such a task. This "threshold" might be different for different tasks and may differ depending on the polarity of GVS. A parametric manipulation of left- and right-cathodal GVS of different current intensities in relation to behavioural tasks as assessed via fMRI might shed light on these issues.

4.3. Implications for neglect rehabilitation

In accordance with previous studies and a recent treatment study (Wilkinson et al., 2014) our results show that GVS is a promising technique for non-invasive, bottom-up stimulation of brain damaged patients with neuropsychological impairments. The technique is easy to administer, low-cost, safe, and has been shown to modulate a wide range of neuropsychological functions transiently (Utz et al., 2010). A recent study showed *lasting* effects of a small number of repetitive GVS sessions on tactile extinction (cf. Schmidt et al., 2013b), thus showing its feasibility and efficacy as a treatment. It is likely that GVS could significantly modulate many other spatial and attentional dysfunctions seen in right-hemisphere lesioned patients, analogous to similar applications in the rehabilitation of motor deficits using transcranial direct current stimulation of the brain (Schlaug, Renga, & Nair, 2008). Future studies should evaluate the stability of GVS effects, the effects of repeated stimulation sessions, polarity, and the effects of combined GVS with other therapeutic techniques such as optokinetic smooth pursuit eye movement training (Kerkhoff, Reinhart, Artinger, Ziegler, Marquardt, & Keller, 2013, Kerkhoff, Bucher, Brasse, Leonhart, Holzgraefe, Völzke, et al., 2014) or theta burst stimulation (Cazzoli, Müri, Schumacher, von Arx, Chaves, Gutbrod, et al., 2012), visuomotor feedback training (Harvey, Muir, Reeves, Duncan, & Rossit, 2010, Harvey, Hood, North & Robertson, 2003). to improve the outcome of neurologically disabled patients.

4.4. Limitations of the study

As a limitation of our study, we cannot completely rule out practice effects as sham stimulation was always administered first. However, some of our findings argue against that possibility: First, our analysis of the spatial bias in number cancellation (CoC) shows a significant *deteriorating* effect of left-cathodal GVS in the RBD- group which is not indicative of practice effects. Second, the RBD- group showed no effect in any condition in the line bisection task. Instead, there was a constant *leftward* line bisection error above 0 that should have been reduced if test repetition would have had an effect. In addition, except for line bisection, none of the tasks was given twice to the same patient to limit order effects. Taken together, even if we cannot completely rule out the contributing effects of test practice, these appear unlikely.

Figures, Legends

<u>Figure 1:</u> Schematic display of the four experimental neglect tests (see text for further details).

<u>Figure 2:</u> Results of Galvanic Vestibular Stimulation (GVS) on number cancellation (A) and copying of symmetrical figures (B) across the three experimental conditions (Sham=Baseline; Cathode Left, Cathode Right). *: $p < .05$. Error bars indicate 1 SEM (Fig. A) or 1 SD (Fig. B). CoC values close to +1 indicate a severe rightward neglect in a patient who only cancelled the rightmost targets (and vice versa for a score of -1). See text for details.

<u>Figure 3:</u> Results of Galvanic Vestibular Stimulation (GVS) on horizontal line bisection (A) and text copying (B) across the three experimental conditions (Sham=Baseline; Cathode Left, Cathode Right). *: $p < .05$. Error bars indicate 1 SEM (Fig. A) or 1 SD (Fig. B). See text for details.

<u>Table 1:</u> Patient characteristics of 24 patients with unilateral right-hemispheric stroke.

Patient	Age/ Sex	Etiology	Lesion	TSL (months)	Hemi-paresis	Field Defect	NC	CSF	HLB	TC
RBD-1	55/m	I	F, T	4	p	a	+	x	+	+
RBD-2	76/m	I	F, T, P	84	p	HH	+	+	+	+
RBD-3	65/m	I	F, T, P, BG	3	p	Q	-	+	+	+
RBD-4	65/m	I	T	15	p	a	+	+	-	+
RBD-5	70/f	H	BG	2	p	a	+	+	+	+
RBD-6	62/m	I	T	1	p	a	+	+	+	+
RBD-7	59/m	I	P, O	1	a	a	+	+	+	+
RBD-8	72/f	I	T	2	p	HH	-	+	+	x
RBD-9	50/m	I	T	2	p	a	-	+	-	x
RBD-10	51/m	I	BG	1	p	a	-	-	-	-
RBD-11	70/m	I	T	1	p	a	-	-	-	-
RBD-12	67/m	I	T, F	1	p	a	+	+	-	+
RBD-13	79/f	I	T, F	2	p	a	+	x	+	x
RBD-14	84/f	I	F, T	12	p	a	-	-	-	-
RBD-15	72/m	I	T, P	1	p	Q	-	-	+	-
RBD-16	70/m	I	T	2	p	a	-	-	-	+
RBD-17	70/m	I	F	35	p	a	+	+	+	+
RBD-18	42/f	I	T, BG	1	a	a	-	+	-	-
RBD-19	76/f	I	F, T, P, O	1	p	HH	+	x	x	+
RBD-20	53/f	I	O	3	a	HH	-	-	-	-
RBD-21	51/m	H	P	1	a	Q	-	-	-	-
RBD-22	57/f	H	T, P	3	p	a	+	+	-	-
RBD-23	67/f	I	F	1	p	a	+	+	+	+
RBD-24	44/m	H	F, T, P	3	p	a	+	+	+	-
	Mean: 63.3 yrs	20 I, 4 H		Median: 2 month	17/24 im-paired	7/24 im-paired	13RBD+ 11 RBD- N=24	14 RBD+ 7 RBD- N= 21	12 RBD+ 11 RBD- N= 23	12 RBD+ 9 RBD- N= 21

<u>Abbreviations</u>: I/H: ischemic/hemorrhagic stroke; P/T/F/O/BG: parietal/temporal/frontal/ occipital/basal ganglia; TSL: time since lesion; HH: homonymous hemianopia, Q: quadrantanopia; p/a: present/absent; NC/CSF/HLB/TC: number cancellation/copy of symmetrical figures/copy of horizontal line bisection/text copying, +/-/x: with neglect in this task/without neglect in this task/not tested in this task.

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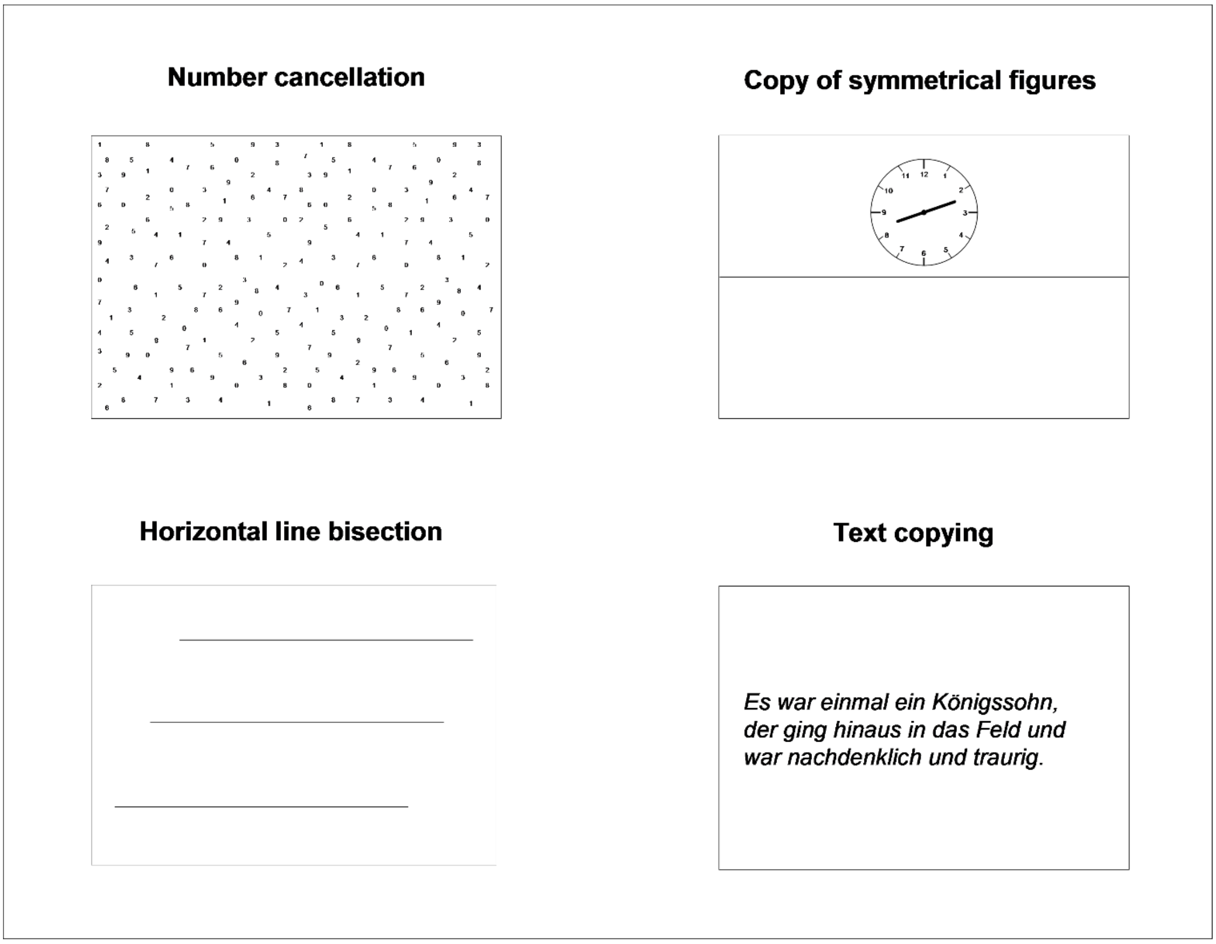
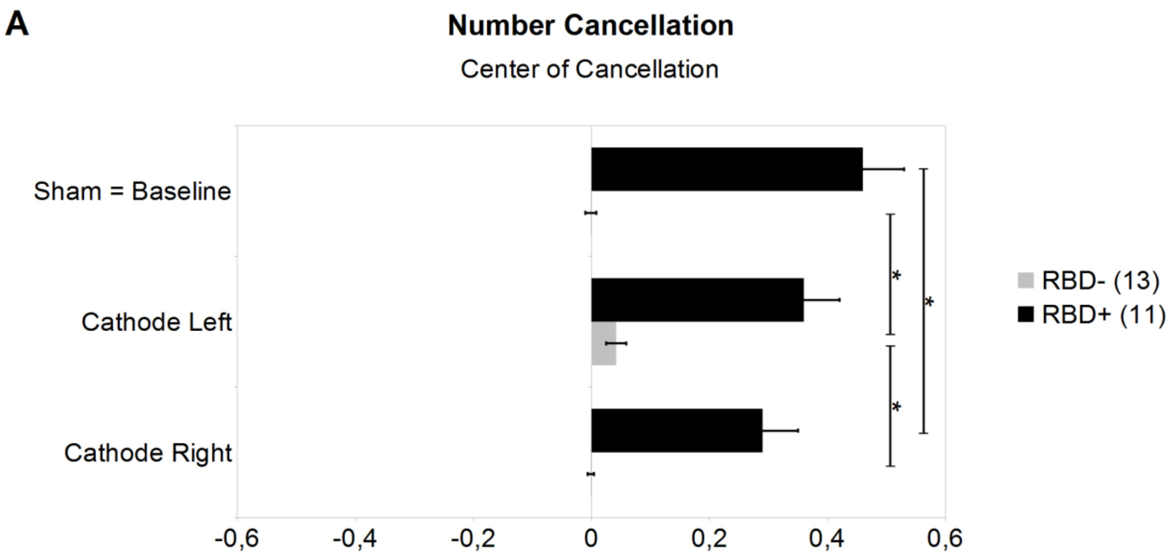

Number cancellation
Copy of symmetrical figures
Horizontal line bisection
Text copying
Es war einmal ein Königssohn,
der ging hinaus in das Feld und
war nachdenklich und traurig.

Fig. 1

Results of GVS on number cancellation (A) and figure copying (B)



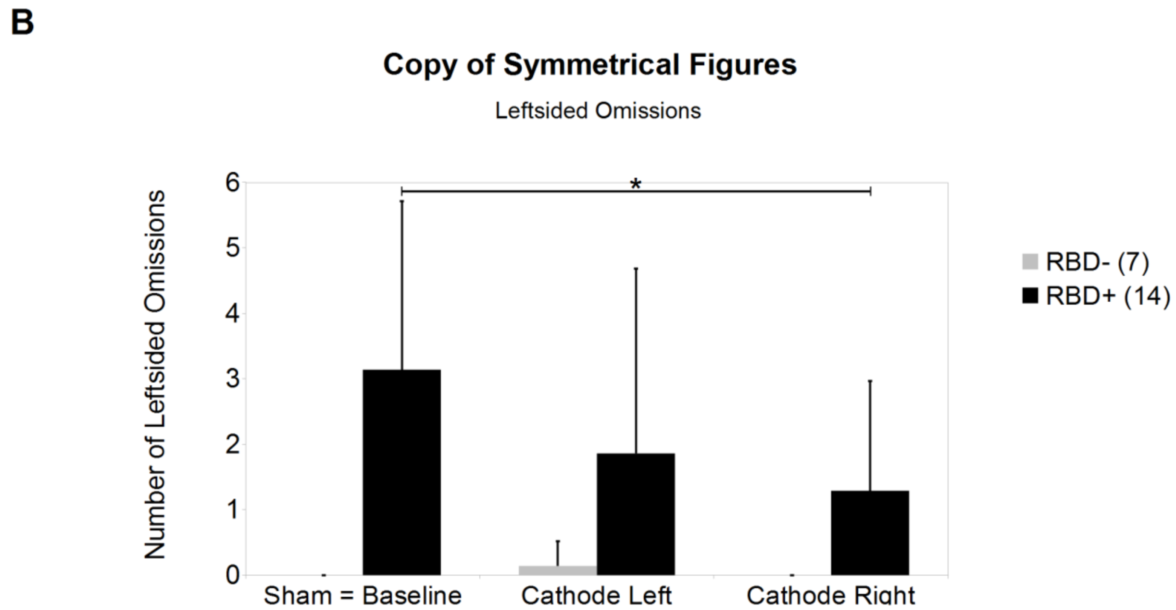
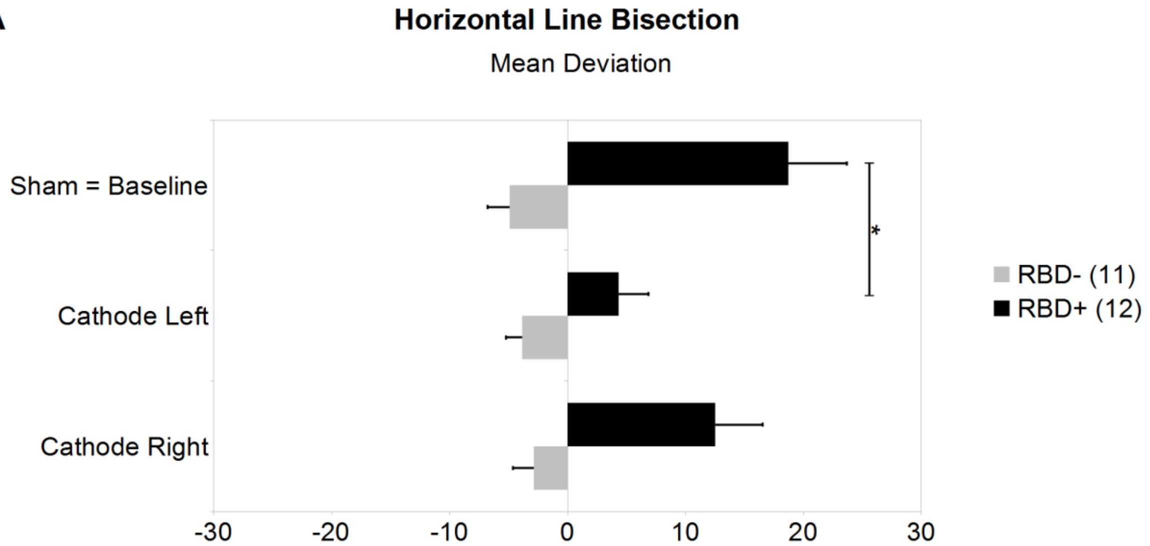


Fig. 2

Results of GVS on horizontal line bisection (A) and text copying (B)

A



B

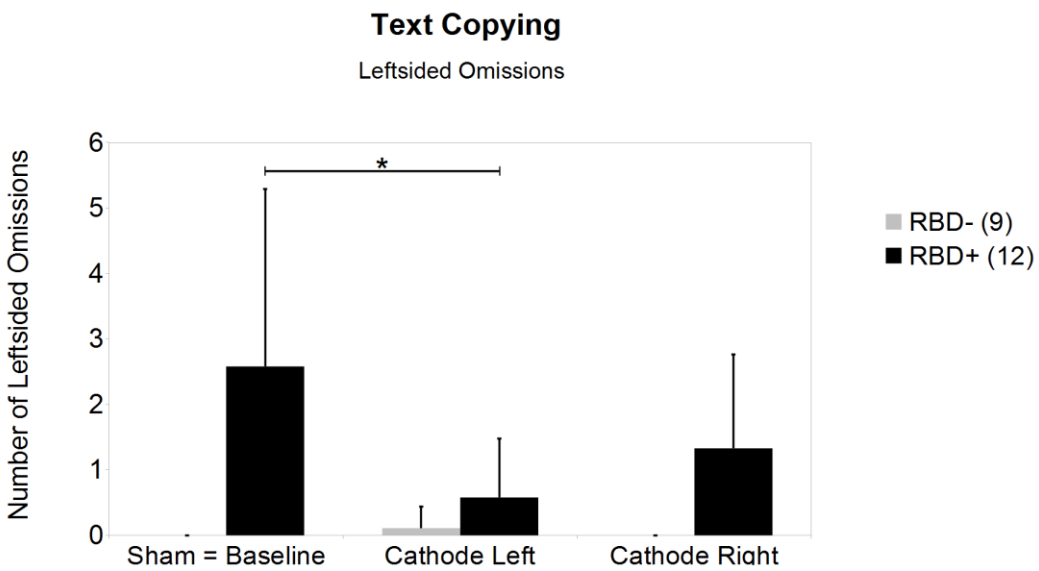


Fig. 3