A long-lasting improvement of tactile extinction after galvanic vestibular stimulation: Two Sham-stimulation controlled case studies

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ABSTRACT

Sensory extinction is frequent and often persistent after brain damage. Previous studies have shown the transient influence of sensory stimulation on tactile extinction. In the present two case studies we investigated whether subliminal galvanic vestibular stimulation (GVS) modulates tactile extinction. GVS induces polarity-specific changes in cerebral excitability in the vestibular cortices and adjacent cortical areas in the temporo-parietal cortex via polarization of the vestibular nerves. Two patients (DL, CJ) with left-sided tactile extinction due to chronic (5 vs. 6 (1/2) years lesion age) right-hemisphere lesions (right fronto-parietal in DL, right frontal and discrete parietal in CJ) were examined. Both showed normal tactile sensitivity to light touch and yielded 90–100% correct identifications in unilateral tactile stimulations for both hands. In Baseline investigations without GVS and Sham-GVS both showed stable left-sided tactile extinction rates of 40–55% (DL) and 49–72% (CJ). In contrast, one session of right-cathodal GVS (intensity: 0.6 mA, duration: 20 min) permanently improved tactile identification of *identical* stimuli, while a second session with left-cathodal GVS significantly reduced left-sided extinction rates for *different* stimuli in DL. Patient CJ's left-sided tactile extinction was significantly improved by left-cathodal GVS (0.5 mA, 20 min) for *different* stimuli, while right-cathodal GVS induced a significant reduction for *identical* materials. In contrast, Sham-stimulation was ineffective. Improvements remained stable for at least 1 year (DL) resp. 3 weeks (CJ). Control experiments ruled out improvements in tactile extinction merely by retesting. In conclusion, chronic tactile extinction may be permanently improved by GVS in a polarity-specific way.

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1. Introduction

Extinction of sensory stimuli is defined as the inability to process or attend to the more contralesionally located stimulus when two stimuli are simultaneously presented. By definition, the processing of a single stimulus should be only marginally impaired, thereby ruling out gross elementary sensory deficits (i.e. hemianopia, hemi-anaesthesia, unilateral hearing loss). Extinction may occur in the visual (Conci et al., 2009), auditory (Deouell & Soroker, 2000), olfactory (Eskenazi, Cain, Novelly, & Friend, 1983) or tactile modality

(Berti et al., 1999; Maravita et al., 2003). Tactile extinction is frequently found after unilateral, mostly right sided brain lesions (70%, Heldmann, Kerkhoff, Struppler, Havel, & Jahn, 2000; Schwartz, Marchok, & Flynn, 1977; Schwartz, Marchok, Kremers, Kreinick, & Flynn, 1979) and often persists for years after the lesion (Heldmann et al., 2000). Causative lesions are found in the frontal, parietal, or temporal cortex (Deouell & Soroker, 2000; Schwartz et al., 1977), and the basal ganglia (Vallar, Rusconi, Bignamini, & Geminiani, 1994). In addition, anterior callosal lesions may disrupt the processing of the left-hand tactile stimulus (Schwartz et al., 1979) which may explain the more frequent occurrence of tactile extinction on the left body side than on the right (Schwartz et al., 1979). Moreover, tactile extinction does not only occur when the patient has to *detect* tactile stimulation (Bender, 1952), but also appears when she/he has to *discriminate* different tactile surfaces (Schwartz et al., 1977), and even occurs when a patient explores simultaneously two common household objects actively by touch (Berti et al., 1999). Tactile extinction is modulated by stimulus properties (i.e. additional sensory stimulation of the hand) *and* response factors

(verbal vs. nonverbal output, cf. Vaishnavi, Calhoun, Southwood, & Chatterjee, 2000). The latter indicates that interference between both stimuli can even occur at a post-perceptual level, probably close to the language system.

Two main explanations of extinction have been proposed: sensory (Bender, 1952) and attentional theories (Vallar et al., 1994). While the prior explain extinction as the result of a weakened sensory integration process the latter hold that elementary sensory abilities may be completely intact, and yet extinction occurs. In favour of the latter account several studies have shown that early sensory or preattentive processes are often reasonably intact in patients with visual extinction (Conci et al., 2009). Various stimulation manoeuvres such as caloric vestibular stimulation (Vallar, Bottini, Rusconi, & Sterzi, 1993), optokinetic stimulation (Nico, 1999), repetitive peripheral magnetic stimulation (Heldmann et al., 2000), and visuomotor prism adaptation (Maravita et al., 2003) significantly modulate tactile extinction. This accords with proposals that somatosensory deficits in right hemisphere patients may relate, at least partially, to neglect (Vallar, 1997), which can be significantly modulated by sensory stimulation manoeuvres (Kerkhoff, 2003). Yet, few studies have so far evaluated to which degree tactile extinction can be *permanently* cured with such methods. A recent case study (Dijkerman, Webeling, ter Wal, Groet, & van Zandvoort, 2004) reported a long-lasting (for at least 1–3 weeks), beneficial effect of only two sessions of prism-adaptation on somatosensory functions (pressure sensitivity and proprioception), indicating a considerable potential for the treatment of these disorders.

Galvanic vestibular stimulation (GVS) is a powerful, easy to apply technique of non-invasive vestibular stimulation (Utz, Dimova, Oppenlander, & Kerkhoff, 2010), which produces only few side effects in difference to *caloric*-vestibular stimulation (Utz et al., revision). Practically, GVS consists of applying direct current, usually delivered by a small battery-driven constant current stimulator, by attaching two electrodes of different polarities (one anode and one cathode) to the two mastoids behind the ear. On the neural level, GVS induces polarization effects in the vestibular nerves, leading to an activation of the semicircular canals, otolith organs and the adjacent vestibular nerves (Fitzpatrick & Day, 2004). Cortical activation is seen in the posterior insula and the temporo-parietal region, the prior being considered as the human homologue of the parieto-insulo-vestibular cortex (PIVC) of the monkey (Brandt, Dieterich, & Danek, 1994). Further activation was found in the middle and superior temporal gyrus, the putamen, the anterior cingulate gyrus and thalamus (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998). Interestingly, the cerebral activation pattern after left-cathodal and right-cathodal GVS is asymmetric in the human vestibular cortices. Placing the cathode behind the right ear (right-cathodal GVS) induces inhibition of the left and excitation of the right vestibular nerve, followed by *unilateral* activation of the right vestibular and parietal cortex as well as in adjacent areas. In contrast, placing the cathode behind the left ear (left-cathodal GVS) inhibits the right and excites the left vestibular nerve which in turn induces *bilateral* activations of the vestibular and parietal cortex, as well as in adjacent areas (Fink et al., 2003). The activations induced by GVS are similar to those induced by caloric vestibular stimulation (see Section 4.2, below).

Only a few studies have so far evaluated the potency of GVS in patients with neglect, extinction and related spatial disorders. In a first, pioneering study Rorsman, Magnusson, and Johansson (1999) have shown a transient reduction of visual neglect symptoms in patients with neglect (i.e. line cancellation) during right-cathodal GVS. A recent case study found a significant improvement in visuo-constructive deficits (copy of Rey-figure) during GVS (Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010). Another study (Saj, Honore, & Rousseaux, 2006) reported online-effects of left-cathodal GVS on the counterclockwise tilt of the subjective visual vertical in patients with visual neglect.

As outlined above, GVS induces polarity-specific activation of the brain. As tactile extinction is viewed by some theories (Schwartz et al., 1979) as a result of an imbalance of sensory inputs received simultaneously from both hands we hypothesized that GVS may influence tactile extinction via activations of the vestibular cortices and adjacent temporoparietal cortices in the brain. From the available literature on GVS we expected a *transient* reduction of left-sided extinction errors under GVS, but no specific effect on right-sided errors induced by GVS. Regarding polarity we had no directional hypothesis as some of the few available GVS studies showed improvements during *left*-cathodal GVS, others during *right*-cathodal GVS (as mentioned above). In the present case studies we therefore explored the effects of GVS on tactile extinction in two patients with a chronic (5 vs. 6 (1/2) years post lesion), right hemispheric lesion. Apart from *online*-stimulation effects we were interested in the after-effects of GVS and potential enduring effects on tactile extinction.

2. Materials and methods

2.1. Case histories

Patient DL, a male, 70 year old, strongly righthanded former restaurant cook (laterality score of +100 in the German version of the Edinburg handedness inventory, Salmaso & Longoni, 1985) had suffered from a large right intracerebral bleeding at the age of 65. DL had received 10 years of schooling. Magnetic resonance imaging (MRI) showed a right superior frontal lesion, including right parietal white matter and a small portion of the corpus callosum, and additionally an old small thalamus infarct in DL's left hemisphere (Fig. 1). In the early months after the lesion DL had shown contralesional, left-sided visual neglect in conventional clinical tests and during his daily behavior. All investigations reported here took place 5 years after the lesion. At this time DL showed no visual field defect, a residual hemiparesis of his left body side, but could walk with a walking-stick. He had normal tactile sensitivity for light touch on his left and right body side. He was unimpaired in elementary visuospatial tests (subjective visual vertical, line orientation, position discrimination, Kerkhoff & Marquardt, 1998), but showed stable left-sided extinction of tactile stimuli during *bilateral* stimulation, combined with a normal *unilateral* sensitivity for the same stimuli. There were no other signs of visual neglect as DL's performance was normal in the following tests: 0 omission on the left and right side in a number cancellation task (Kerkhoff, 2000), only 3 mm deviation to the left side in horizontal line bisection (normal cutoff: ±5 mm to either side, Kerkhoff, 2000), normal copy of a clock face, 40th percentile in the Judgment of Line Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983). DL showed no aphasia or apraxia and no unawareness of his left-sided hemiparesis. DL had received physical therapy in the last 3 years prior to investigation and continued to receive 2 weekly sessions (à 30 min) for his left hemiparesis throughout the *complete* course of this study. As the frequency remained constant this cannot account for the changes in extinction reported below.

The second patient, CJ, was a female, 43 year old, right-handed (laterality-score of +100) cook in a hospital cantine with 9 years of schooling. CJ had suffered in December 2003 from a spontaneous rupture of the right trunk of the anterior communicating artery aneurism with subsequent subarachnoideal hemorrhage (Hunt and Hess grade 2). The aneurism was clipped with a Yasargil Miniclip. The acute cCT scan showed massive bleed in the subarachnoid space of both hemispheres including the basal cisterns. During the treatment on the intensive care unit and after the clipping of the aneurysm CJ suffered at least from one additional vasospasm. The neurosurgical operation approached from the right hemisphere via the sylvian fissure. Postoperatively, CJ suffered from a residual left-sided hemiparesis, cognitive and emotional disturbances, a residual left-sided neglect (in cancellation tasks) and extinction. Despite stationary and ambulatory rehabilitation treatment for several years, CJ finally had to retire 3 years after the clipping of the hemorrhage. At the time of investigation, CJ showed a chronic, discrete, left-sided visual neglect and tactile extinction, as well as an incomplete left-sided, homonymous hemianopia (field sparing: 10° on the left horizontal axis). She had normal tactile sensitivity for light touch on her left and right body side. Horizontal line bisection of a 200 mm long line was performed normally (+1% deviation to the right), as was line number cancellation (<2 omissions in left and right hemispace). Figure copy (star, diamond, flower) was also performed normally. However, visual search for targets in CJ's left hemispace was delayed significantly in comparison to the right hemispace. In contrast, CJ's language, reading, praxis, and concentration (at least up to 1 h) were normal at the time of investigations, which all took place 6 (1/2) years after the lesion. At the time of investigation, CJ did not receive any regular therapies during the course of this study, which could influence tactile extinction. Fig. 2A and B shows lesions
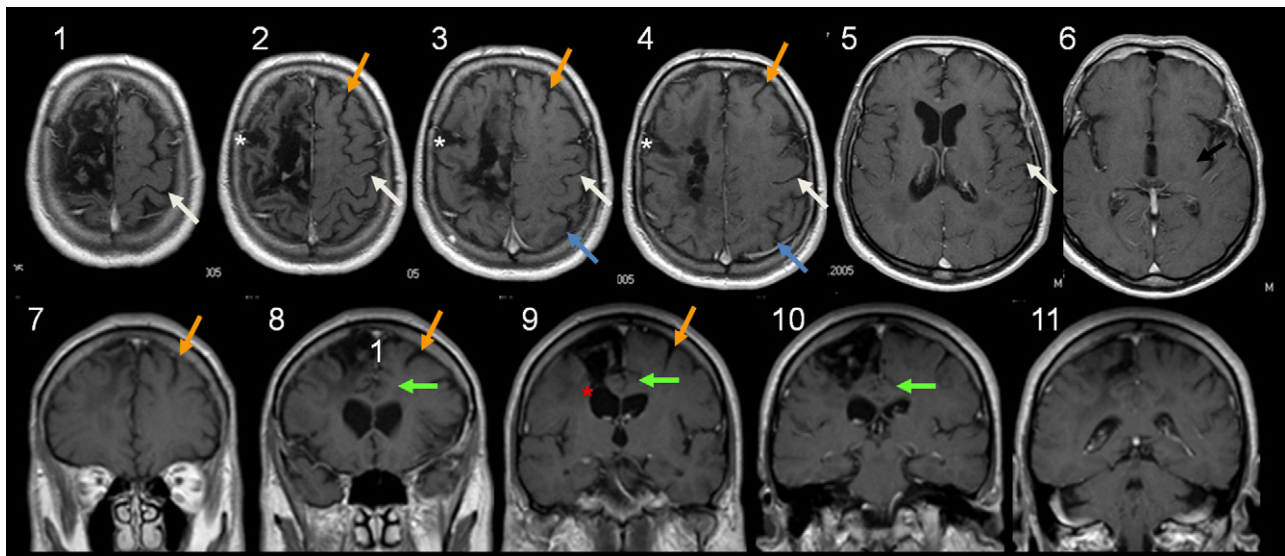
Fig. 1. DL's structural brain lesion 30 months after lesion onset displayed by a T1 magnetic resonance image sequence. The axial (upper row) and the coronal slices (lower row) show a unilateral lesion starting at the central sulcus with some extension into the white matter of the parietal lobe (at least in the T2 images not shown here). The lesion extends anteriorly into the Brodman areas 8 and 6, mainly restricted to the supplementary and pre-supplementary motor cortex. A small shed of the premotor area is also involved (images 2–3, white asterisk). Ventrally, the lesion extends into the corona radiata and touches the cingulate cortex. Above the thalamic nuclei at the level of the corpus callosum the lesion extends ventrally up to the lateral ventricle (red asterisk) and therefore cuts the interhemispheric connections of the corpus callosum. *Legend*: The left hemisphere corresponds to the right half of each brain slice. White arrows: central sulcus; light blue arrows: intraparietal sulcus; orange arrows: superior frontal sulcus; green arrows: cingulate gyrus; black arrow: small left thalamic infarct. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)
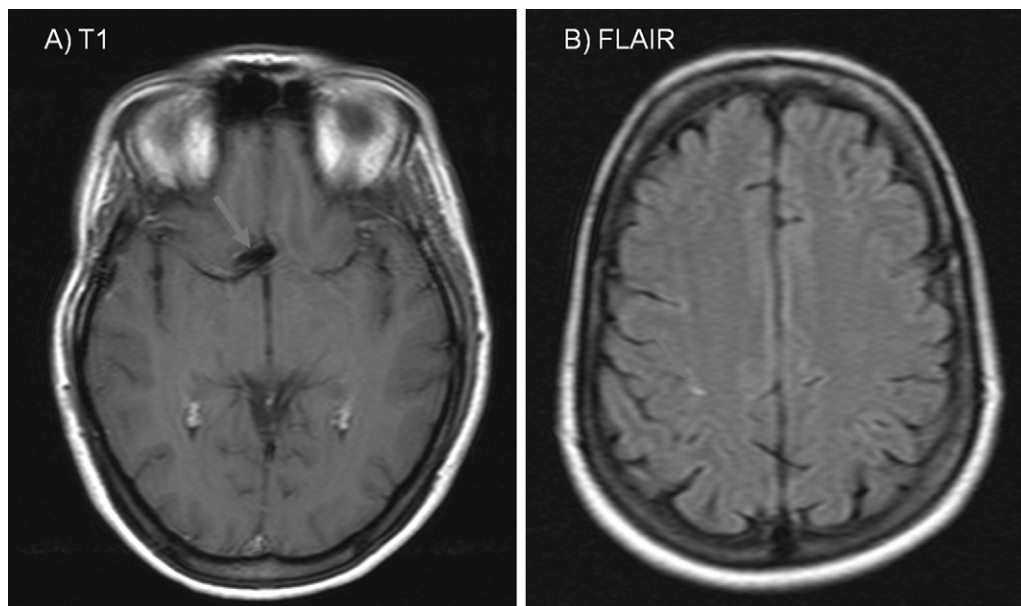
in the right orbitofrontal cortex and a discrete hyperintensity in the right parietal cortex.

2.2. Quality Extinction Test

The Quality Extinction Test (QET; Schwartz et al., 1977) is a sensitive tactile extinction test that requires the subject to identify and name six different tactile surfaces first in unilateral trials on the left and right dorsal palm, and then in double simultaneous stimulation (DSS) trials with the same materials. Previous studies with the QET have shown that patients with right frontal or right parietal lesions consistently show marked left-sided tactile extinction in those trials with *bilateral*

different stimuli while showing normal performance in unilateral target presentations (Schwartz et al., 1977; Schwartz et al., 1979). Subsequent studies with the QET provided evidence that tactile extinction is modulated by somatosensory input delivered via repetitive peripheral magnetic stimulation (Heldmann et al., 2000; Kerkhoff, Heldmann, Struppler, Havel, & Jahn, 2001).

The present version of the QET includes six different materials varying in tactile quality (soft sandpaper, silk, fleece, plastic, jute and rubber gum) that were attached singly to wooden boards (size: 15 cm × 10 cm). Both patients placed their hands with the palms down and beneath each other on the table in front of the experimenter. During all testing sessions the patients were blindfolded and wore a closed headphone in order to prevent visual and auditory cues during the tactile stimulation

Fig. 2. Magnetic resonance images of patient CJ taken 4 (1/2) years after the subarachnoideal hemorrhage. It showed in the T2 weighted sequence at the right medial basis of the orbitofrontal cortex the clip running from the posterior parts of the gyrus rectus into the medial orbitofrontal gyrus. The T1 weighted scans also documented the clip at the right medial orbitofrontal cortex, but no other lesions (A). The FLAIR sequence showed a small hyperintensity in the right parietal white matter just below the hand knob of the central sulcus (B) and again no other lesions. This small hyperintensity was restricted to only one slice of the scan. Arrows indicate the lesioned areas. Note that the left side of the brain in the figure corresponds to the right cerebral hemisphere, while the right side corresponds to the left cerebral hemisphere.

procedure. The patients were instructed to identify and name the six different tactile materials used throughout the test. To this purpose, single boards were moved slowly by the experimenter with a speed of 2 cm/s from proximal to distal across the dorsal palm of either the left or right hand. Each material was presented three times in this way and the patients had to report verbally the material. 18 unilateral trials were run for each hand separately in the two patients, for every measurement date. After these unilateral trials, which served to assess unilateral tactile performance, bilateral stimulation trials were performed. Here, one board was presented simultaneously to each hand and the patient had to name the material(s) he/she recognized on both hands. A total of 36 bilateral trials were performed in each complete test: 18 trials with different and 18 trials with identical material delivered to both hands. Unilateral trials were not repeated during the experimental sessions as this had been done previously before the experimental sessions (including the GVS) and unilateral performance was of no particular interest in this study. Both patients were unaware of the fact that one half of the trials were performed with identical and the other half with different tactile materials as both were intermingled within every session. If the patients could not identify correctly one or both of the materials in a trial with bilateral stimulation, an extinction response was scored for the corresponding side. Thereafter, the next bilateral stimulation trial was performed. No attempt was made, to force the patients to guess in case they were unable to verbally identify the material. Moreover, the patients were not forced to guess whether the two stimuli were same or different in case of missing verbal response for one side. The percentage and raw score of left- and right-sided extinction during double simultaneous stimulation (DSS) with *different tactile stimuli* (based on 18 trials) as well as during DSS with *identical* tactile stimuli (based on the other 18 trials) were computed for every session (see below). Because of the possible interference between the two different tactile materials delivered in those 18 trials with different materials and the requirement to verbally report two materials this task is more difficult than that with the DSS of identical tactile materials (see Section 3.7). Note, that the QET – in contrast to conventional tactile extinction procedures using light touches of the patient's hands – requires *discrimination* of 6 different tactile materials and finally their verbal identification. Therefore, a higher degree of errors may be found, including some ipsilesional errors as well (Heldmann et al., 2000). Data from 15 healthy control subjects (age: 20–75) were available and used for the calculation of cutoff-scores for the left and right hand (shown in Figs. 4–6 as stippled lines).

2.3. Galvanic vestibular stimulation (GVS)

Bipolar galvanic vestibular stimulation was delivered by a constant direct current (DC) stimulator (9 voltage battery, Type: ED 2011, producer: DKI GmbH, DE-01277 Dresden, Germany). The tap water-soaked sponge-covered electrodes (60 mm × 40 mm) were fastened on the skin over each mastoid (binaural stimulation), in order to activate the vestibular system. The condition was termed left-cathodal GVS when the cathode was placed on the left mastoid and the anode on the right, and right-cathodal GVS when polarization was performed inversely. Like Rorsman et al. (1999) we stimulated below the sensation threshold (subliminal) so that the subject is not aware of any electrical stimulation in any experimental or Sham condition (Utz et al., 2010). As there is evidence that even subtle attentional cues can modulate neglect and extinction (Riddoch & Humphreys, 1983), we employed this subliminal stimulation as it elegantly circumvents potential cueing effects that might occur with *supra-threshold* stimulation. During the latter, the subject experiences a tactile sensation under one or both electrodes, which could influence lateralized extinction scores via attentional cueing. A switch on the stimulation device delivered current at an individually adjusted level to the patients. The threshold was determined by slowly increasing current intensity in steps of 0.1 mA until the patient indicated a tingling. Current was then reduced until the patient indicated that the feeling had disappeared. This procedure was repeated a second time and the mean of both threshold values was defined as the threshold. DL's mean threshold was 0.7 mA, therefore we used 0.6 mA current intensity for GVS stimulation in the right-cathodal and left-cathodal experimental condition. The threshold was 0.6 mA in patient CJ, therefore we used 0.5 mA for all GVS stimulations with her. Neither DL nor CJ reported any sensations of the current in these chosen subliminal conditions. These current levels were used in both patients for all real GVS stimulations (left-, or right-cathodal GVS). To rule out potential placebo-stimulation effects we implemented a condition of Sham-stimulation in both patients, as well as a post-test 60 min after Sham-GVS in CJ. Here, the electrodes were attached, the current was turned up until DL or CJ felt the typical tingling sensation, but then the current was softly reduced after 20 s and finally completely turned off, without both patients being aware of this fact. Finally, in all conditions, the GVS stimulator was never visible for the patients. After real and Sham GVS a questionnaire listing possible side-effects (Poreisz, Boros, Antal, & Paulus, 2007) was read to both patients.

All investigations were performed in accordance to the Declaration of Helsinki II. Both patients had given written informed consent before participation in the study. A positive, written ethical approval by the local medical ethical committee of the Saarland was available for the use of subliminal GVS in brain-damaged patients.

2.4. Experimental investigations

In patient DL, six investigations were performed with the QET at six different time-points (TP) in separate sessions (see Fig. 3, top, for an outline of the design):

(1) Baseline without electrodes (no current applied) = TP1.
(2) During Sham stimulation with GVS (electrodes in place, but no current applied) = TP2; performed 1 h after TP1.
(3) During 20 min of right-cathodal GVS-stimulation (0.6 mA, subliminal) = TP3; performed one week after TP2.
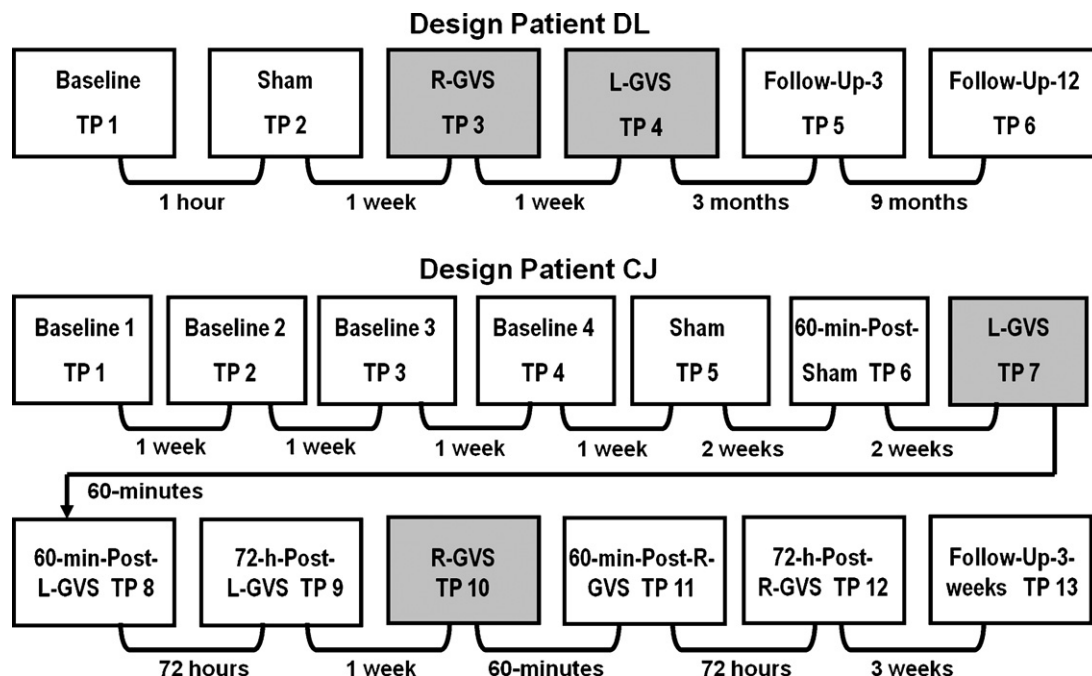
Fig. 3. A schematic overview of the assessments and galvanic vestibular stimulation (GVS) conditions performed with patient DL (top) at 6 different time-points of investigations (TP), and patient CJ (bottom) performed at 13 different time-points of investigations (TP). Abbreviations: L-GVS: left-cathodal GVS, R-GVS: right-cathodal GVS, Sham: Sham-stimulation with GVS but without the application of current; Sham-60-minutes-post-test: post-test 60 min after cessation of Sham-GVS; Follow-Up-3: follow-up 3 months after L-GVS; Follow-Up-12: follow-Up 12 months after L-GVS, Follow-Up-3-weeks: follow-up after 3 weeks; 60-min-Post-L or R-GVS: post-test 60 min after cessation of left- or right-GVS; 72-h-Post-L or R-GVS: post-test 72 h after cessation of left- or right-GVS (see text for further details). The dark shaded boxes indicate the stimulation sessions with verum (real) GVS.

(4) During 20 min of left-cathodal GVS stimulation (0.6 mA, subliminal) = TP4; performed one week after TP3.
(5) Early follow-up (3 months post-stimulation) = TP5; performed 3 months after TP4.
(6) Late follow-up (12 months post-stimulation) = TP6; performed 9 months after TP5.

Hence, the investigations in DL at TP1 and 2 served as measurements without real GVS, those at time-point 3 and 4 were used for the experimental GVS interventions with the application of current, and the assessments at TP5 and 6 served as follow-up investigations without GVS in order to investigate the stability of GVS-effects.

In patient CJ, a similar but slightly more elaborated design was used (Fig. 3, bottom).

(1) Over a period of 2 months, 4 baseline tests without GVS (TP1–4) were run to rule out any spontaneous improvements in extinction (=TP1–TP4).
(2) Sham-GVS (=TP5), performed 2 weeks after TP4.
(3) 60-min post-test after Sham-GVS (=TP6).
(4) During 20 min of left-cathodal GVS (0.5 mA, subliminal) = TP7; performed 2 weeks after TP5.
(5) 60-min post-test after left-cathodal GVS = TP8, performed 60 min after TP7.
(6) 72-h-post-test after left-cathodal GVS = TP9, performed 72 h after TP8.
(7) During right-cathodal GVS (0.5 mA, subliminal) = TP!, performed 1 week after TP.
(8) 60-min post-test after right-cathodal GVS = TP1!, performed 60 min after TP10.
(9) 72-h-post-test after right-cathodal GVS = TP12, performed 72 h after TP11.
(10) 3-week-follow-up = TP13, performed 21 days after TP12.

The additional 60-min and 72-h post-tests after left- and right-cathodal GVS were employed in patient CJ to evaluate the question of immediate after-effects and potential changes between the real (left- or right-cathodal) GVS stimulation sessions over a longer time window as it was done in patient DL. The 3-week-follow-up was the latest possible follow-up in CJ for completion of this manuscript revision. However, a long-term follow-up after 3 and 12 months is planned in CJ as was done in DL.

2.5. Statistics

Non-parametric statistical analyses (Siegel, 1976) were computed separately in both patients (SPSS, version 17). The single raw scores in the QET in each of the experimental investigations were used for statistical investigations (separately for each hand). Friedman-Tests were run to test for a general difference in extinction scores across all experimental conditions, separately for the left and right hand. Subsequent paired comparisons were performed with Wilcoxon tests with an alpha-level of 0.05, two-tailed, adjusted for the number of comparisons according to Holm (Holm, 1979). Here, the first paired comparison is run with alpha (0.05), the second with alpha/2, the third comparison with alpha/3 and so on.

3. Results

3.1. Unilateral trials (patients DL and CJ)

In the 108 unilateral trials (18 unilateral trials per measurement × 6 measurements) patient DL scored 92% correct for his right hand and 88% correct for his left hand. In the 234 unilateral trials (18 unilateral trials per measurement x 13 measurements) patient CJ scored 95% correct in unilateral trials of her left hand, and 94% of her right hand.

3.2. Bilateral different tactile stimuli (patient DL)

Non-parametric analysis of variance revealed a significant difference between the left-sided extinction scores on the 6 different experimental investigations (Friedman-Test, $X^2 = 28.750$, $df = 5$, $p < 0.0001$), and the right hand ($X^2 = 17.059$, $df = 5$, $p < 0.004$). Subsequent paired comparisons with Wilcoxon tests for the *left-sided* extinction scores revealed no significant difference between the initial Baseline and the Sham-GVS-condition ($z = -1.0$, $p > 0.05$), but a significant difference between left-cathodal GVS and Baseline ($z = -2.828$, $p < 0.005$), and between left-cathodal GVS and Sham-GVS ($z = -2.646$, $p < 0.008$). Moreover, left-sided extinction errors at the 3-month-follow-up ($z = -2.449$, $p < 0.05$) and at the 12-month-follow-up ($z = -2.828$, $p < 0.05$) were significantly lower than during
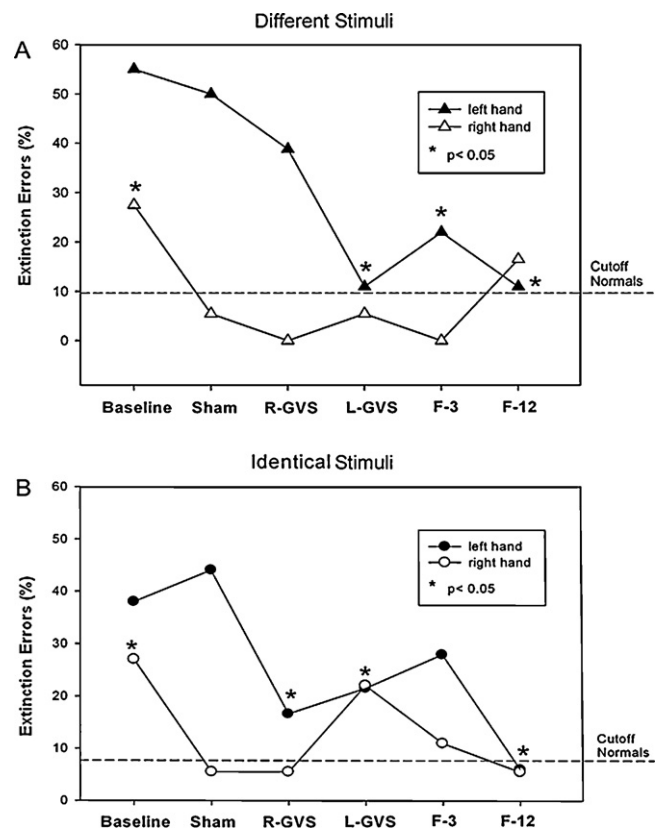
Fig. 4. *Top*: DL's extinction scores during bilateral simultaneous stimulation with *different* tactile materials (in %) for the left and right hand in six experimental investigations with the Quality Extinction Test with and without galvanic vestibular stimulation (GVS; see text for details). L-GVS: left-cathodal GVS; R-GVS: right-cathodal GVS; Sham: electrodes attached, without current: Note the significant reduction of left-sided extinction scores during left-cathodal GVS, while right-cathodal GVS had no significant effect. The improvement remained stable in the 3-month and 12-month-follow-up investigation. *Bottom*: DL's extinction scores (in %) during bilateral simultaneous stimulation with *identical* tactile stimuli. The experimental conditions and abbreviations are the same as in the top figure. Note the reduction of extinction for identical tactile stimuli after right-cathodal and left-cathodal GVS when compared to Baseline and Sham-conditions. Asterisks indicate that this value differs significantly from other values with $p < 0.05$, two-tailed, corrected for multiple comparisons (see text for details).

baseline. Performance during left-cathodal GVS and three-month-follow-up did not differ significantly ($z = -1.414$, $p > 0.05$), and between left-cathodal GVS and 12-months-follow-up did not differ either ($z = 0$, $p > 0.05$). Performance during right-cathodal GVS did not differ significantly from Baseline or Sham-GVS (both $p > 0.05$).

Wilcoxon tests for the *right-sided* extinction scores showed only two significant results: the initial baseline score was significantly higher than that during Sham-GVS ($z = -2.0$, $p < 0.05$), and than that during right-cathodal GVS ($z = -2.23$, $p < 0.05$). There were no significant differences between any of the other right-sided extinction scores when adjusted (largest $z = -1$, smallest $p = 0.317$).

In sum, only left-cathodal GVS significantly reduced left-sided tactile extinction errors for different materials, this effect remained stable in both follow-up investigations. No effect of GVS was observed for the right-sided extinction scores, but there was a significant improvement from the Baseline to Sham-GVS condition with no further change (Fig. 4).

3.3. Bilateral identical tactile stimuli (patient DL)

Non-parametric analysis of variance (Friedman-Test) revealed a significant difference between the extinction scores on the 6 dif-
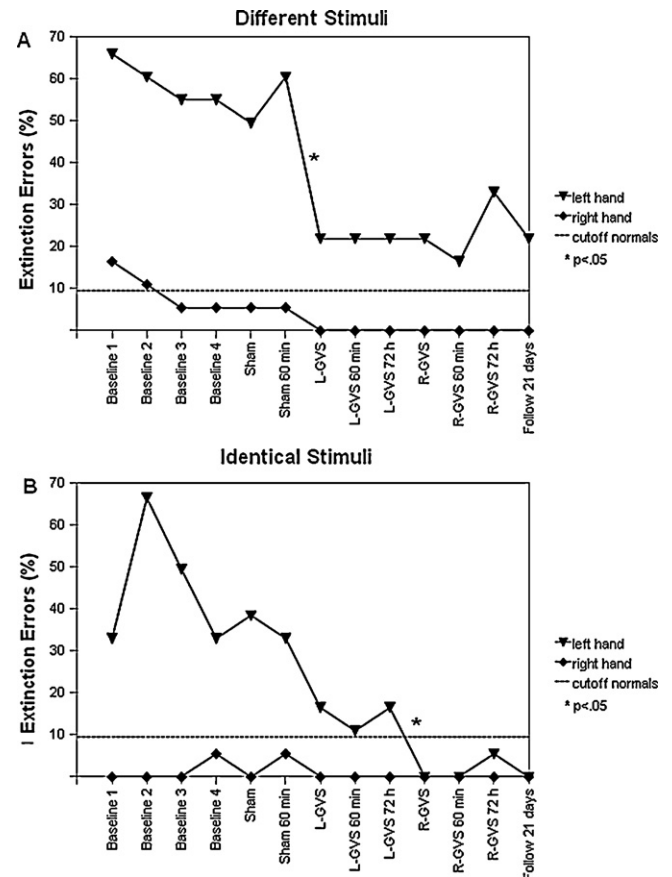
ferent experimental investigations for the left side ($X^2 = 20.833$, $df = 5$, $p > 0.001$), and the right side ($X^2 = 15.333$, $df = 5$, $p < 0.009$). Subsequent paired comparisons with Wilcoxon tests for the left-side extinction scores revealed no significant difference between the initial Baseline and the Sham-GVS-condition ($z = -1.0$, $p > 0.05$), but a significant difference between left-cathodal GVS and Baseline ($z = -2.0$, $p < 0.05$), and between right-cathodal GVS and Sham ($z = -2.236$, $p < 0.05$), as well as between right-cathodal GVS and Baseline ($z = -2.0$, $p > 0.05$). No significant change was found between left- and right-cathodal GVS ($z = -1$, $p > 0.05$), so that no further improvement from right-cathodal GVS (TP3) to left-cathodal GVS (TP4) was found. Performance at the 3-month-follow-up was not significantly different from left-cathodal GVS ($z = -1$, $p > 0.05$) and right-cathodal GVS ($z = -1.414$, $p > 0.05$). Likewise, performance at 12-month-follow-up was not significantly different from performance during left-cathodal GVS ($z = -1.732$, $p > 0.05$) and during right-cathodal GVS ($z = -1.414$, $p > 0.05$). Left-sided extinction errors were significantly lower at the 12-month-follow-up investigation ($z = -2.449$, $p < 0.05$) but not at the 3-month-follow-up measurement ($z = -1.414$, $p > 0.05$). All other paired comparisons failed significance after alpha-adjustment.

Paired comparisons for the *right-hand* extinction scores showed that the Baseline- and Sham-GVS-scores differed significantly ($z = -2.0$, $p < 0.05$). Likewise, extinction scores during right-cathodal GVS differed significantly from the Baseline ($z = -2.0$, $p < 0.05$). All other comparisons failed significance after alpha-adjustment (largest $z = 1.732$, smallest $p = 0.083$). Hence, there was only a significant improvement from Baseline to Sham for the right-sided extinction-scores.

To summarize, right-cathodal GVS significantly reduced *left*-sided tactile extinction errors. This improvement remained stable during left-cathodal GVS at TP4 and at both follow-up tests (TP5 and TP6). Neither left- nor right-cathodal GVS had a significant effect on *right-hand* extinction scores, but test performance improved significantly from the initial Baseline test to Sham-GVS (Fig. 4).

3.4. Bilateral different tactile stimuli (patient CJ)

Non-parametric analysis of variance revealed a significant difference between the left-sided extinction scores on the 13 different experimental investigations (Friedman-Test, $X^2 = 72.316$, $df = 12$, $p < 0.0001$), and as well between the right-sided extinction scores ($X^2 = 22.105$, $df = 12$, $p < 0.036$). A subsequent analysis compared the four baselines for the left- and right-sided extinction scores and found no significant differences for either the four left-sided baseline scores ($X^2 = 4.714$, $df = 3$, $p > 0.05$) or the right-sided scores ($X^2 = 4.714$, $df = 3$, $p > 0.05$). We therefore computed an averaged baseline score for the left and right side for subsequent paired comparisons. In a next step we run paired comparisons with Wilcoxon tests against the averaged baseline scores for the left-sided and right-sided extinction scores separately. These analyses revealed that CJ's left-sided extinction scores during left-cathodal GVS differed significantly from averaged baseline ($z = 2.686$, $p < 0.008$). Moreover, left-sided extinction scores during Sham-GVS did not differ significantly from averaged baseline scores ($z = -1.64$, $p > 0.05$), nor did left-sided extinction scores at the 60-min-post-Sham measurement differ significantly from averaged baseline scores ($z = -.447$, $p > 0.05$). Furthermore, left-sided extinction scores during left-cathodal GVS were not significantly different from all other left-sided measurements taken *after* the left-cathodal GVS, including the 60-min-post-test after left-cathodal GVS and all later obtained scores for the left side up to the final 3-week-follow-up (smallest $p = 0.30$). No other paired comparison reached significance when using Holm's sequential rejective Bonferroni correction, see above.

Fig. 5. *Top*: CJ's extinction scores during bilateral simultaneous stimulation with *different* tactile materials (in %) for the left and right hand in six experimental investigations with the Quality Extinction Test with and without galvanic vestibular stimulation (GVS; see text for details). L-GVS: left-cathodal GVS; R-GVS: right-cathodal GVS; Sham: electrodes attached, without current: Follow-Up-3-weeks: follow-up after 3 weeks; 60-min-Post-L or R-GVS: post-test 60 min after cessation of left- or right-GVS; 72-h-Post-L or R-GVS: post-test 72 h after cessation of left- or right-GVS; Sham-60-minutes-Post-test: post-test 60 min after cessation of Sham-GVS (see text for further details). Note the significant reduction of left-sided extinction scores during left-cathodal GVS, which was maintained until follow-up. Right-cathodal GVS had no significant effect. *Bottom*: CJ's extinction scores (in %) during bilateral simultaneous stimulation with *identical* tactile stimuli. The experimental conditions and abbreviations are the same as in the top figure. Note the significant reduction of left-sided extinction for identical tactile stimuli after right-cathodal, but not after left-cathodal GVS when compared to Baseline and Sham-GVS. Asterisks indicate that this value differs significantly from other values with $p < 0.05$, two-tailed, corrected for multiple comparisons (see text for details).

The initial significant result in the Friedman Test for the right-sided errors most likely stemmed from a slight decrease in extinction rates from the first to the third baseline which however did not differ significantly when compared over the 4 baselines as already mentioned above.

Right-sided extinction scores during left-cathodal GVS did not differ significantly from averaged baseline scores ($z = -1.64$, $p > 0.05$), although the graph in Fig. 5 shows some decline in the error rate (by some 7%) during left-cathodal GVS.

In summary, left-sided extinction scores for different stimuli were significantly and selectively reduced during the application of left-cathodal GVS in patient CJ. This beneficial effect was maintained from this stimulation, over the immediate 60-min-post-test, over all consecutively taken measurements up to the follow-up after 3 weeks (see Fig. 5, top). Right-cathodal GVS and Sham-GVS did not influence left-sided extinction scores significantly.

3.5. Bilateral identical tactile stimuli (patient CJ)

Non-parametric analysis of variance (Friedman-Test) revealed a significant difference between the extinction scores on the 13 different experimental investigations for CJ's left-sided extinction scores ($X^2 = 65.239$, $df = 12$, $p > 0.0001$), but not for her right-sided extinction scores ($X^2 = 12.0$, $df = 12$, $p > 0.05$). A subsequent analysis compared the four left-sided extinction scores in Baselines 1–4 and found a significant difference ($X^2 = 19$, $df = 3$, $p < 0.0001$). This result was largely due to the increase in the extinction rate in Baseline 2 (see Fig. 5, bottom). In order to obtain an average baseline measure for subsequent comparisons, we then computed an average baseline score based on Baseline 1, 3 and 4 (excluding Baseline 2), which did not differ significantly from each other ($X^2 = 6$, $df = 2$, $p > 0.05$). In a next step we run paired comparisons with Wilcoxon tests against this averaged left-sided baseline score. These analyses revealed that CJ's left-sided extinction scores obtained during Sham-GVS ($z = -1.732$, $p > 0.05$) or from that taken at 60-min-post-Sham-GVS ($z = -1$, $p < 0.05$) did not differ significantly from averaged baseline scores before the GVS intervention. Likewise, left-sided extinction scores obtained during left-cathodal GVS did not differ significantly from averaged baseline ($z = -1.473$, $p > 0.05$), nor did this score differ significantly from that taken during Sham-GVS ($z = -1$, $p > 0.05$) or that taken at 60-min-post-Sham-GVS ($z = .441$, $p > 0.05$).

In contrast, left-sided extinction scores were significantly reduced during right-cathodal GVS as compared to averaged baseline ($z = 2.762$, $p < 0.006$) and also when compared to the preceding score of 72-h-post-test after left-cathodal GVS ($z = 2.008$, $p < 0.045$). No other paired comparison reached significance when alpha-corrected.

To summarize, left-cathodal GVS failed to improve significantly left-sided extinctions scores when compared against averaged baseline scores—despite a trend in this direction as can be seen in Fig. 5. However, the subsequent application of right-cathodal GVS *did* significantly reduce left-sided extinction scores, both in comparison to the preceding measurement and to averaged baseline scores. This improvement remained stable until follow-up after 3 weeks. Sham-GVS had no significant immediate or after-effect on left-sided extinction. Right-hand performance showed a floor-effect (almost no errors), without any significant modulation by GVS.

3.6. Side effects

A systematic questionnaire regarding side effects of direct current stimulation (adapted from Poreisz et al., 2007), which included items about fatigue, dizziness, vision and sleep disturbances, concentration difficulties, pain, skin disturbances, burning sensations, etc. (cf. Utz et al., revision) was orally read to both patients after all GVS stimulations. DL reported no side effects in any of the 34 items after left- or right-cathodal GVS, nor after Sham-stimulation. CJ reported a transient increase in loudness of her tinnitus after GVS, which after some hours normalized to pre-stimulation levels. No other side effects were reported by CJ in any of the stimulation conditions. Moreover, no skin burns, seizures, vertigo or nausea were observed nor reported during or after the GVS-sessions in DL and CJ.

3.7. Control experiment

One relevant aspect of our study is the potential influence of retesting effects on extinction performance. In addition, DL's unexpected improvement in *right*-hand extinction scores from the baseline- to the Sham-measurement, while no such effect was seen for his left ("extinguishing") hand was puzzling. This prompted us to investigate potential practice effects arising from test repetition
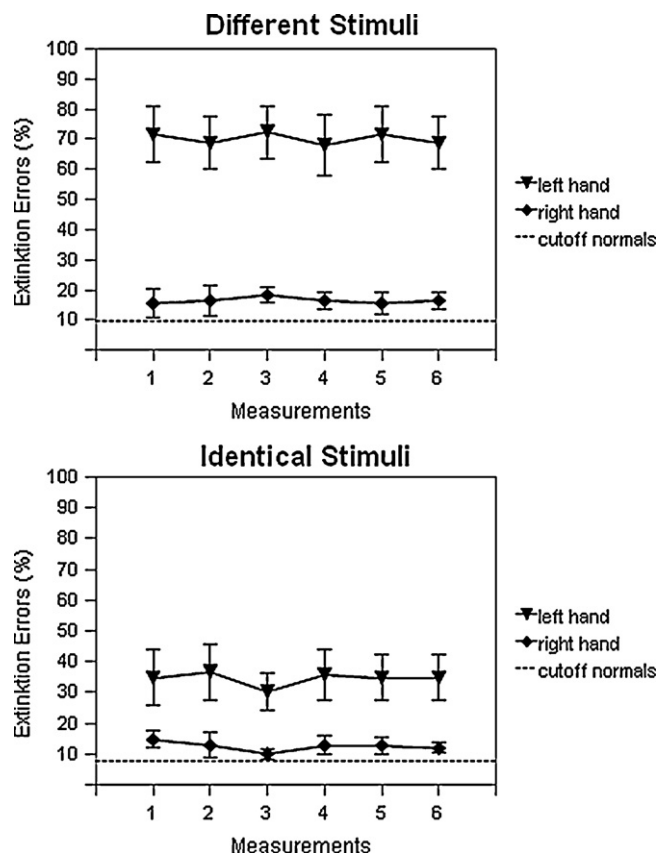
Fig. 6. Mean (±standard error of the mean) extinction errors (%) for the left and right hand in the Quality Extinction Test of six patients with chronic left-sided tactile extinction (see text and Table 1 for details) across six repetitive measurements. The upper figure displays the results during the application of *different* tactile stimuli in the QET, the lower figure those during the application of *identical* tactile stimuli in the QET. Dotted lines indicate the cutoff limit of normal control subjects in the two tasks. Note that apart from moderate variations in error rates no significant improvement was observed in any of the four graphs due to retesting in 6 subsequent sessions.

without GVS for the left and right hand in the QET. Six additional patients with chronic left-sided tactile extinction due to a single right hemispheric brain lesion were investigated to this purpose. Four of the patients had suffered – like DL and CJ – a right-sided intracerebral bleeding. Age varied from 25 to 68, with 3 male and 3 female subjects (Table 1). These patients were tested six times with the QET in the same way as DL and CJ. The time intervals between the first four time points were identical to those of DL and CJ. However, the interval between measurement 4 and 5 and 5 and 6 was set at 1 month for every interval in order to save time. No GVS or other specific therapy was applied in these six patients.

Fig. 6 shows similar extinction rates of the six patients in the QET for different and identical tactile stimuli as both DL and CJ. Nonparametric (Friedman test) analysis of ranks showed no significant improvement across the six test repetitions with the QET for the left-sided scores obtained in the QET with *different* materials ($X^2 = 6.677$, $df = 5$, $p = 0.246$), nor for the right-sided scores obtained with *different* materials ($X^2 = 0.695$, $df = 5$, $p = 0.983$), nor for the left-sided scores with *identical* materials ($X^2 = 4.114$, $df = 5$, $p = 0.533$), nor for the right-sided scores with *identical* materials ($X^2 = 2.682$, $df = 5$, $p = 0.749$). Hence, test repetition did not lead to any improvements in tactile extinction in six comparable patients with tactile extinction, regardless of whether they had *severe* left-sided tactile extinction (cases 1–5, error rates of 60–80%) or only *moderate* extinction (case 6, error rate of 25–33%).

Another interesting result is evident from this control experiment: tactile extinction is significantly more severe (as shown

Table 1
Clinical and demographic data of six patients with chronic, left-sided extinction due to a right-hemispheric brain lesion; ICB: intracerebral bleeding. Visual neglect: diagnosis based on conventional tests of cancellation, line bisection, figure copy and reading; tactile extinction: as tested by tactile stimulation of the patient's hand surface by touch.

Patient	Age, sex	Aetiology	Lesion, lesion age (months)	Motor deficits	Visual field	Visual neglect	Tactile extinction
1-ME	59, male	ICB	Right fronto-parietal, 5	Left hemiparesis	Normal	No	Severe
2-TA	47, female	ICB	Right Basal Ganglia, 12	Left hemiparesis	Normal	Yes	Severe
3-CR	68, male	Posterior cerebral artery infarction	Right thalamus and right occipital, 5	No	Left hemianopia	Yes	Severe
4-WI	45, male	Middle cerebral artery infarction	Right parietal, 15	Left hemiparesis	Left lower quadranopia	Yes	Severe
5-TU	47, female	ICB	Right parietal, 5	Left hemiparesis	Left lower quadranopia	Yes	Severe
6-HA	25, female	ICB	Right basal ganglia, 11	No	Normal	No	Minor

by higher error rates in the QET) when *different* tactile stimuli have to be discriminated on the left hand (mean: 71.7%) as compared to the condition with identical tactile stimuli (mean: 34.8%; Wilcoxon-test, $z = -2.201$, $p < 0.028$, two-tailed). No such difference was obtained for the right hand (mean error rate for different vs. identical stimuli: 15.6% vs. 14.7%, $z = -0.271$, $p > 0.05$, n.s.).

4. Discussion

Three main findings are apparent from our study: (1) GVS can modulate tactile extinction significantly in a polarity-specific way, even in a very chronic stage. (2) A small number of GVS sessions may be sufficient to induce lasting changes in tactile extinction that remain stable for at least 3 weeks (patient CJ), or even one year post-stimulation (patient DL). (3) These findings are unlikely to arise from retesting as no such effects were observed in any of 6 additional patients with chronic left-sided tactile extinction, nor was there any spontaneous improvement in extinction over 4 successive baseline tests prior to the GVS stimulation in patient CJ. As a side note, no (patient DL) or only minimal and transient side effects (patient CJ) were noted in our study.

4.1. Mechanisms of GVS on tactile awareness

Left-cathodal GVS significantly reduced left-sided tactile extinction in the identification of *different* tactile surfaces delivered during DSS, while it had only a smaller nonsignificant effect on left-sided extinction errors for identical materials. The opposite pattern of results was obtained for right-cathodal GVS: this stimulation significantly reduced left-sided extinction errors for identical tactile materials, while it induced a smaller, nonsignificant reduction of left-sided extinction errors for different materials. How can these findings be explained?

The greater efficiency of *left*-cathodal as compared to *right*-cathodal GVS is probably due to the fact that the former induces *bilateral* activation of the cortical vestibular system whereas the latter induces only *right-sided* activation of the cortical vestibular system (Fink et al., 2003), centring on the PIVC and adjacent areas in the parietal and temporal cortex. Due to the anatomical asymmetry of the vestibular system (Bartenstein et al., 1998) left-cathodal GVS produces a more widespread brain activation than right-cathodal GVS, which results in a stronger modulatory effect on extinction. As clearly shown in the control experiment and stated in the description of the QET (see Section 2.2) it is more difficult to identify (among 6 different materials) and name *two different* materials than two *identical*. In the latter condition the subject even may adopt an implicit (even unconscious) strategy where she/he decides that if both stimulations were "comparable" both materials must represent the same material. This strategy is not applicable during DSS with different tactile stimuli. We do not know whether such a mechanism was at work since both patients denied having used such a strategy during the testings. Nevertheless, it seems plausible to assume that right-cathodal GVS is strong enough to modulate

extinction in *identical* trials but only left-cathodal GVS leads to such a strong bi-hemispheric activation that it can influence extinction in the more demanding condition with *different* tactile materials in the QET. Moreover, it is tempting to relate the improvements for different materials in the QET to the fact that left-cathodal GVS activates perisylvian cortices in *both* hemispheres, hence also in the language-related areas of the left-perisylvian cortex of both patients presumably engaged in the verbal output during extinction testing. In accordance with this hypothesis the inventors of the Quality Extinction Test used in this study proposed that "during the tactile extinction tests a response mechanism in the left (speech) hemisphere bases its perceptual output on the relative strengths of two simultaneous inputs. Damage at any point in the channel from the periphery to the response mechanism weakens one signal in comparison to the other, resulting in a response bias favouring the stronger stimulus" (Schwartz et al., 1979: p. 681f).

Alternatively or additionally, GVS may speed up tactile discrimination learning during DSS, which however does not seem to take place during mere test repetitions *without* GVS, as seen in Fig. 6. This may reflect another interesting and testable hypothesis for future studies as somatosensory deficits and extinction are frequently encountered after brain damage. Whatever the precise mechanism of improvement induced by GVS our results are compatible with the hypothesis that left-cathodal GVS permanently changed the relative strengths of the tactile inputs from both hands. This may result either from an enhancement of left-hand-input and/or a reduction of right-hand-input. As a caveat, it should be mentioned that we cannot be sure whether our patients – DL with a chronic right frontal, and parietal white matter lesion and CJ with a right frontal and discrete parietal lesion – show the same pattern of brain activation in functional imaging as healthy subjects do when receiving GVS. Moreover, as GVS had similar beneficial effects on left-sided tactile extinction in both of our patients despite their different brain lesions, it appears that the activation effects induced by GVS do not rely on a particular lesion area in order to occur.

A limitation of our study was that we did not include a Baseline test without GVS *between* the right- and left-cathodal GVS sessions (between TP3 and TP4) in the first patient studied (DL). This would have allowed us to assess potential after-effects after right-cathodal GVS at TP3. The reason for this was that we did not expect such strong and enduring effects after such a small number of GVS-sessions on tactile extinction in DL, and therefore were primarily interested in online-effects *during* GVS. We therefore implemented a more sophisticated design including time-points to investigate after-effects of 60 min to 72 h after the two real GVS-session (left-cathodal, right-cathodal) in the second studied patient that was studied here (CJ). Her data clearly show an after-effect of left-cathodal GVS on tactile extinction lasting for at least 72 h, after which we moved on to the other experimental GVS-condition (right-cathodal GVS). As in DL, CJ's extinction scores remained significantly improved after only two real GVS-sessions. The additional time-points in CJ show that there is a nearly perfect after-effect after left-cathodal GVS for different materials (Fig. 5,

top, left-hand-curve), but no further improvement, nor any positive after-effect after right-cathodal GVS. Note, that CJ could have further improved by right-cathodal GVS in extinction for different materials up to the level of the normal subjects, since her left-sided extinction score was still around 20% left-hand errors while the cut-off level of the normal control subjects was at 12%. The situation is different for identical stimuli: here we see a significant reduction of left-sided extinction errors only after right-cathodal GVS, which is maintained after both stimulations for at least 72 h and then persists until follow-up. Interestingly, there was also a numerical reduction of the left-sided extinction errors by some 15 5 induced by left-cathodal GVS, as well as a further improvement at the 60-min-post-test after left-cathodal GVS. However, none of these numerical improvements reached significance when alpha-adjusted. Hence, CJ's result –despite their very different brain lesion – mirror neatly those obtained in patient DL in so far as left-cathodal GVS induced significant reductions in left-sided tactile extinction for *different* materials while right-cathodal GVS significantly reduced left-sided extinction errors for *identical* materials.

Another relevant issue is the sequence of GVS-sessions with different polarities and their influence on the test results. A recent study employing transcranial direct current stimulation in healthy subjects suggests that polarity of stimulation and the sequence of stimulation sessions may influence learning (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009). We therefore reversed the sequence of the two real GVS-sessions with different polarities in patient CJ in comparison to patient DL in order to control for the sequence effect. Despite the different sequences, the data obtained are highly consistent, as mentioned above. Moreover, because of the differences in brain lesions in both patients (see Figs. 2 and 3) it appears unlikely that the beneficial effect of GVS on tactile extinction depends on damage to a particular area in the right hemisphere. Subsequent studies might evaluate the efficiency of *repetitive* left- vs. right-cathodal GVS on extinction to further investigate the role of different polarities. Importantly, our control experiment showed that mere test repetition does not lead to any significant improvements in the order of some 30–40% as shown here for the left hand of both patients.

From a methodological point of view, it is important to note that Sham-GVS had no measurable effect nor did it induce any after-effect on tactile extinction, thus ruling out unspecific effects of the stimulation procedure. A slight, non-significant improvement was shown during Sham-GVS in DL, while a greater, also nonsignificant deterioration in extinction was observed during Sham-GVS in CJ. Moreover, as stimulation was performed below the sensory threshold in both patients, subtle attentional cueing effects (Riddoch & Humphreys, 1983) merely as a result of the tingling sensation when the current stimulates the (left) mastoid can also be ruled out as an explanation of our results. Finally, the small but significant improvement of DL's performance on his right-hand scores from the initial Baseline to Sham (see Fig. 4) most likely reflects a nonspecific learning effect, i.e. due to some kind of adaptation to the general test procedure. It is important to note however, that the improvements observed under GVS for DL's *left* side were not related to any improvements in extinction for his right side. Put differently: the left-hand decline in extinction errors under GVS was not due to a potential attentional shift that might be indicated by a simultaneous increase of right-sided extinction errors. Right-sided errors in CJ were completely within normal limits for identical stimuli, and did not change significantly over time for different stimuli.

4.2. Vestibular cortex and vestibular stimulation

Neurophysiological studies in primates all have indicated the parietal lobe as the main projection area of vestibular input. Electri-

cal stimulation of the vestibular nerve showed a cortical projection to Brodman area 2 (Schwarz & Fredrickson, 1971) and evoked potentials showed cortical activations in Brodman area 3 (Ödkvist, Schwarz, Fredrickson, & Hassler, 1974). Functional imaging studies using caloric vestibular stimulation show activations in areas of the perisylvian cortex including the insula and retroinsular cortex, the temporoparietal cortex, the putamen, somatosensory area II (Bottini et al., 2001), as well as in the intraparietal cortex (Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Suzuki et al., 2001). In accordance with these activations, numerous studies using caloric vestibular stimulation have shown a beneficial influence on neglect and neglect-related disorders such as extinction (Vallar et al., 1993), somatoparaphrenia (Rode et al., 1992) or unawareness of hemiplegia (for review see Vallar et al., 2003). In summary, the cortical and subcortical effects of caloric and galvanic vestibular stimulation are rather similar, but subliminal GVS as used here is likely to circumvent the behavioral side effects of caloric vestibular stimulation such as nystagmus, vertigo and dizziness and their possible influence on task performance (Bottini et al., 2001).

4.3. Stability of GVS-effects

The observed improvements after GVS remained stable for at least 3 weeks after 2 real GVS sessions in patient CJ, and for at least 1 year post-stimulation in patient DL. As spontaneous recovery can be ruled out 5 years (DL) or 6 (1/2) years (CJ) post-lesion and no other specific therapy was performed in parallel in both patients the observed improvements most likely result from the GVS intervention. A particular interesting, qualitative impression was that during GVS an almost immediate improvement was observed in both patients (more so for left-cathodal GVS) from the very first trials in the test, and no adaptation was observed throughout the 36 trials. Hence, it appears that the neuromodulatory effect of GVS was instated rather quickly after application (within 1–2 min of stimulation). This finding may have practical relevance for treatment studies as it may indicate rapid changes, including the observed, lasting after-effects found here. In agreement with our present results a recent single case study (Dijkerman et al., 2004) found substantial and immediate improvements in somatosensory functions in a patient with a right temporo-parietal and basal ganglia lesion after 1–2 sessions with prism adaptation which remained stable for at least 1–3 weeks post-stimulation. Moreover, five 20-min-sessions of direct current stimulation (1 mA intensity) over the primary motor cortex of patients with subcortical stroke improved motor function by 7.3–9.5%, and remained stable at a 2-week-follow-up (Boggio et al., 2007). Although our present data clearly require verification in larger patient samples, they suggest a considerable potential of GVS in the rehabilitation of related disorders, such as visual extinction (Conci et al., 2009), motor neglect or unawareness of paresis (Rode, Perenin, Honoré, & Boisson, 1998).

5. Conclusions

Two 20-min-sessions of subliminal GVS had a significant effect on tactile extinction in two patients with chronic right-hemisphere brain lesions and enhanced tactile awareness permanently on their contralesional body side, up to a level of postsensory processing of the bilateral tactile input onto a verbal output level. As subliminal GVS produces few or no side effects (Utz et al., revision) it may be more convenient – especially for *repetitive* stimulations – than *caloric*-vestibular stimulation which may cause adverse effects like vertigo, dizziness and nystagmus (Bottini et al., 2001). Moreover, subliminal GVS is painless, noninvasive, safe, easily applicable and elegantly allows the realization of placebo/Sham-stimulation without the patient being aware of any stimulation or of cessation

of stimulation. This makes it a promising tool for future research, including treatment studies.

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