

# Influence of the stimulus parameters of galvanic vestibular stimulation on unilateral spatial neglect

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Galvanic vestibular stimulation (GVS) stimulates the vestibular system electrically with low-amplitude direct current through surface electrodes applied to the left and right mastoids. The effects of GVS on unilateral spatial neglect (USN) in poststroke patients were recently reported, but the influence of the current intensity and application duration of GVS on USN has not been sufficiently investigated. Here we explored the influence of these stimulus parameters on USN. We recruited seven patients with right-hemisphere stroke and left-sided USN (four female) for this single-blind, sham-controlled cross-over trial. Their scores on the line cancellation test were measured under three stimulation conditions [left-cathodal/right-anodal GVS (L-GVS), right-cathodal/left-anodal GVS, and sham] at three time points (before the start of GVS, 10 min after the start of GVS, and 20 min after the start of GVS). The GVS intensity was set below the sensory threshold and differed among the patients (0.4–2.0 mA). The cancellation scores were significantly increased after 10 and 20 min L-GVS, with a greater increase observed after

the latter ( $P < 0.0001$ ). The other stimulus conditions had no significant effect. There was a significant positive correlation between the change in the increase in the cancellation score with L-GVS and the total charge ( $r = 0.81$ ,  $P = 0.0004$ ). The effect of GVS on USN may depend on its application duration, current intensity, and polarity. *NeuroReport* 26:462–466 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

*NeuroReport* 2015, 26:462–466

**Keywords:** cancellation test, electrical stimulation, galvanic vestibular stimulation, spatial neglect, stroke, vestibular stimulation

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Received 24 December 2014 accepted 16 March 2015

## Introduction

Unilateral spatial neglect (USN) has been defined as the failure to report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion, when this failure cannot be attributed to either sensory or motor defects [1]. Patients with USN perform worse on tests of activities of daily living at both admission and discharge, and typically spend significantly longer in rehabilitation hospitals, compared with patients without USN [2,3]. The presence of USN adversely affects functional recovery, and USN rehabilitation strategies that are practical for use in clinical settings are needed.

Karnath and Dieterich [4] found that both USN and vestibular processing at the cortical level involve common brain areas, and USN may thus be closely related to the dysfunctions of the integrated vestibular system. The caloric vestibular stimulation (CVS) technique involves the irrigation of the ear canal with either cold or warm water. CVS has shown a beneficial influence on USN and related disorders [5,6]. Despite its short-term effectiveness, CVS has not been evaluated as a tool for long-term or repetitive stimulation, because CVS is often accompanied by negative side effects such as nystagmus and vertigo.

A more convenient vestibular stimulation technique is galvanic vestibular stimulation (GVS), which is associated with few side effects. GVS is low-amplitude direct current electrical stimulation applied to the left and right mastoids through surface electrodes to stimulate the vestibular system [7,8]. GVS induces polarization effects on the otoliths and semicircular canal afferents [9]. Modulation of the firing activity of the vestibular nerve is achieved by cathodal or anodal stimulation to increase or decrease the firing frequency, respectively [9,10]. A difference in the placement of the electrodes may thus affect the efficacy. Utz *et al.* [11] suggested that left-cathodal/right-anodal GVS (L-GVS) and right-cathodal/left-anodal GVS (R-GVS) significantly reduced the rightward line bisection error in USN patients. A larger decrease in the rightward line bisection error was also observed during R-GVS. In addition, previous studies suggested that GVS affects electroencephalographic activity [12] and vertical perception [13] in a dose-dependent manner.

It is possible that the effect of GVS on USN depends on the current intensity, application duration, and stimulus polarity. However, the effects of the stimulus parameters of GVS used to improve USN have not been sufficiently

investigated. We hypothesize that manipulation of the current intensity and application duration should be sufficient to improve USN. The aim of the present study was to investigate the influence of the stimulus parameters of GVS on USN.

## Patients and methods

We recruited seven patients with right-hemisphere stroke and left-sided USN (four female) for this single-blind, sham-controlled cross-over trial (Table 1). The patients were recruited from among inpatients who had been admitted to a rehabilitation hospital. The inclusion criteria were an episode of a first-ever hemiparetic stroke, diagnosis of right-hemisphere damage, right-handedness, age 30–89 years, and evidence of left-sided USN based on the Japanese version of the conventional Behavioral Inattention Test (BIT) [14]. The cutoff value for the BIT was set at 131 points for the conventional test (maximum score 146), and individuals scoring below the cutoff value were considered to have USN. The exclusion criteria were the presence of bilateral or left-sided lesions, aphasia, inability to sit in a wheelchair, extremely impaired eyesight, severe cognitive impairment (Mini-Mental State Examination [15], MMSE score < 16), inability to understand the meaning of the study, and vestibular disorders in addition to specific GVS exclusion criteria (presence of a heart pacemaker, pregnancy, metallic brain implants, epilepsy, and sensitive skin behind the ears).

The study design was approved by the hospital's Ethics Review Board. All patients gave their informed written consent to participate in the study, and the study conformed to the principles outlined in the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network Clinical Trial Registry.

## Assessment

We evaluated each patient's USN by conducting the line cancellation test as included in the BIT. For the line cancellation test (score range from 0 to 36 points), the patient was presented with a single sheet of paper on which six lines in varying orientations were drawn. When administering the test, the examiner demonstrated the

nature of the task to the patient by crossing out four lines located in a central column, and then instructing the patient to cross out all of the lines he or she saw on the page. Left-sided USN was indicated by a failure to mark more lines on the left side than on the right.

## Galvanic vestibular stimulation

We applied bipolar GVS using an electrical stimulation system (Chattanooga Intellect Advanced Combo; DJO Global, Vista, California, USA). Two surface self-adhesive electrodes (32 mm × 32 mm) were put on the patient's skin over each mastoid. The stimulus conditions were set at three conditions for each patient: L-GVS, R-GVS, and sham condition. The intensity was set below the sensory threshold so that the patient was not aware of any electrical stimulation. The threshold was determined by increasing the current intensity slowly in steps of 0.1 mA until the patient indicated feeling a tingling sensation. The current was then reduced until the patient indicated that the feeling had disappeared. This threshold level differed between patients at a range of 0.4–2.0 mA. In the sham condition, the two electrodes were positioned as in the R-GVS, except that no electric current was applied. The GVS was delivered for 20 min per condition. During the GVS, the patient sat in a wheelchair. The intensity and duration of the GVS adhered to the safety criteria for transcranial direct current stimulation [16].

## Design and procedure

All patients underwent the three different stimulation conditions in a pseudorandomized sequence to avoid order effects. The patients were blinded to the stimulation conditions received. A 48-h interval was established between sessions to avoid carryover effects. For each session, the patient performed the line cancellation test before, at 10 min, and at 20 min after the start of the GVS (10 and 20 min).

## Statistical analyses

The normal distributions of all data were tested by the Kolmogorov–Smirnov test. A two-way repeated-measures analysis of variance was used to compare the effects of Condition (L-GVS, R-GVS, and sham) and Time (before,

**Table 1** Demographic and clinical data for the patients with unilateral spatial neglect

	Age, sex	Days since stroke	Lesion type	Lesion location	BIT conventional test	MMSE	Current intensity
Patient 1	77, F	240	H	P, Put	15	20	2.0
Patient 2	65, M	143	I	T, P, Put	41	21	2.0
Patient 3	63, F	122	H	P, Put	67	16	1.6
Patient 4	81, M	105	H	Th	19	16	1.0
Patient 5	86, F	138	H	Th	121	23	0.4
Patient 6	83, M	113	H	Put	66	16	0.5
Patient 7	72, F	221	I	P, CR	93	24	0.5
Mean (SD)	75.4 (9.0)	154.8 (53.8)			60.3 (38.4)	19.4 (3.5)	1.1 (0.7)

BIT, Behavioral Inattention Test; CR, corona radiata; F, female; H, hemorrhage; I, infarction; M, male; MMSE, Mini-Mental State Examination; P, parietal lobe; Put, putamen; ST, temporal lobe; Th, thalamus.

10, and 20 min) on the line cancellation score. A post-hoc test with the Holm–Sidak test was used in multiple comparisons. Pearson's correlation coefficient was used to examine the relation between the amount of change in the line cancellation score, the conventional BIT score, and the total charge [total charge as expressed by current density  $\times$  total stimulation duration (s)] in L-GVS and R-GVS. The amount of change from the 'before' line cancellation score was calculated for the 10 and 20 min time points after GVS line cancellation scores. A significance level was set at less than 5%. All statistical analyses were performed with GraphPad Prism 6 (GraphPad Software Inc., San Diego, California, USA).

## Results

All patients completed the study, and no adverse effects were reported. All data were normally distributed. There was no significant difference in the line cancellation scores before stimulation among the stimulus conditions (mean score in L-GVS 24.0, SD=10.5; R-GVS 24.0, SD=10.3; sham 26.0, SD=8.9;  $P=0.78$ ). Repeated-measures analysis of variance showed a significant main effect of Time [ $F(2,36)=6.54$ ,  $P=0.004$ ] and the Condition  $\times$  Time interaction [ $F(4,36)=4.43$ ,  $P=0.005$ ]. In the L-GVS condition, the mean line cancellation score was 26.9 (SD=8.2) in the 10 min GVS and 29.0 (SD=7.0) in the 20 min GVS. Post-hoc testing showed that the line cancellation scores were significantly increased following 10 and 20 min of L-GVS, with a greater increase observed following the latter (post-hoc before vs. 10 min;  $P=0.017$ , before vs. 20 min;  $P<0.0001$ , 10 vs. 20 min;  $P=0.04$ ). In the R-GVS condition, the mean line cancellation score was 25.4 (SD=9.6) in the 10 min GVS and 26.3 (SD=9.9) in the 20 min GVS. The R-GVS condition did not significantly change the line cancellation score (post-hoc before vs. 10 min;  $P=0.32$ , before vs. 20 min;  $P=0.09$ , 10 vs. 20 min;  $P=0.41$ ). In the sham condition, the mean line cancellation score was 24.6 (SD=8.9) in the 10 min GVS and 25.1 (SD=10.4) in the 20 min GVS. The sham condition did not significantly change the line cancellation score (post-hoc before vs. 10 min;  $P=0.43$ , before vs. 20 min;  $P=0.65$ , 10 vs. 20 min;  $P=0.65$ ).

Figure 1 shows the individual line cancellation test results of all patients. All patients except patient 1 showed an increase or maintained the score after the 20 min GVS, which was the most pronounced in the L-GVS. Patient 1 showed great improvement not only in the L-GVS but also in the R-GVS (Fig. 1).

Pearson's correlation coefficient between the conventional BIT and the amount of change in the line cancellation score on L-GVS was  $-0.67$  ( $P=0.008$ ). The correlation between the conventional BIT and the amount of change in the line cancellation score on R-GVS was weak and not statistically significant ( $r=-0.17$ , and  $P=0.55$ ).

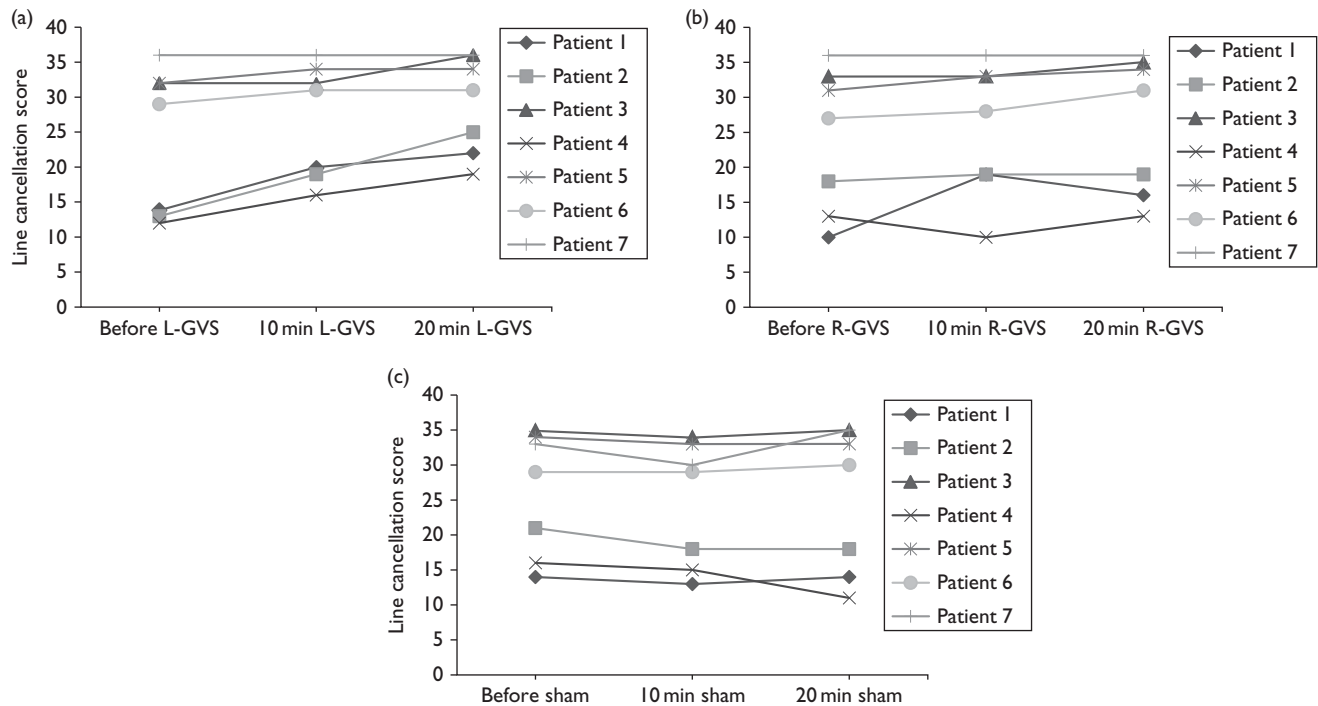
Figure 2 shows the relation between the amount of change in the line cancellation score and the total charge in each polarity. Pearson's correlation coefficient between the amount of change in the line cancellation score on L-GVS and the total charge was  $0.81$  (Fig. 2a,  $P=0.0004$ ). The correlation between the amount of change in the line cancellation score on R-GVS and the total charge was weak and not statistically significant (Fig. 2b,  $r=0.29$ , and  $P=0.32$ ).

## Discussion

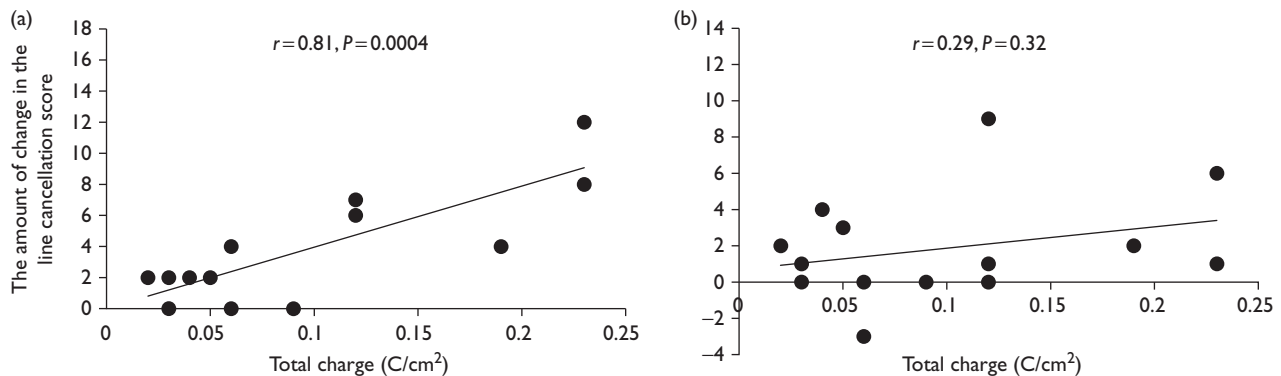
The novel finding of the present study is that the line cancellation scores were significantly increased after 10 and 20 min L-GVS, with a greater increase observed after the latter. There was also a significant positive correlation between the amount of change in the line cancellation score after L-GVS and the total charge. The higher current intensity used for patients 1, 2, and 3 (1.6–2.0 mA) might have been more effective for the treatment of USN compared with the other patients (0.5–1.0 mA). Our data demonstrate that the effect of GVS on USN as measured by the line cancellation test depends on the application duration and on the current intensity and polarity of GVS. To our knowledge, the present study is the first to explore the dose-dependent effects of GVS on USN. Our results suggested that, to treat USN, a higher intensity and longer application duration in the L-GVS condition should be used. However, higher current intensity is associated with more frequent adverse effects compared with subsensory level intensity [17], and it is thus necessary to monitor the possible adverse effects in patients.

There was a significant negative correlation between conventional BIT and the amount of change in the line cancellation score on L-GVS. The USN of patients 1, 2, and 4 was more severe than that of other patients. These severely affected patients showed great improvement after 20 min L-GVS. GVS may thus be an effective treatment method for severe USN patients. In the present study, patients 3, 5, and 7 were able to score more than 30 points in the line cancellation test before each GVS. Although a ceiling performance on the line cancellation test was easily reached in these patients, the cancellation tests have shown good test–retest reliability and was shown to be more sensitive for detecting USN than the line bisection test [18,19].

With regard to polarity, in contrast to the results of the present study, Utz *et al.* [11] suggested that R-GVS compared with L-GVS had a greater beneficial effect on line bisection error in USN patients. A probable reason for the differing effects could be the different lesion locations examined in this study. In a previous study [11], many of the patients had suffered a cortical lesion, whereas a few patients who had suffered a lesion in the subcortical region, such as the basal ganglia and thalamus, showed remarkable improvement in L-GVS. Unlike that

**Fig. 1**

Individual scores on the line cancellation test under each condition for the seven patients with unilateral spatial neglect. (a) The left-cathodal/right-anodal galvanic vestibular stimulation (L-GVS) condition. (b) The right-cathodal/left-anodal GVS (R-GVS) condition. (c) The sham condition.

**Fig. 2**

Correlation between the amount of change in the line cancellation score and the total charge in each polarity condition for patients with unilateral spatial neglect. (a) The left-cathodal/right-anodal galvanic vestibular stimulation (L-GVS) condition. (b) The right-cathodal/left-anodal GVS (R-GVS) condition.

study, many patients of our study had suffered a lesion in a basal ganglia, such as the putamen. USN following a subcortical lesion centering on the right basal ganglia is caused by dysfunction of the perisylvian network [20]. The perisylvian network densely connects the inferior parietal lobule, superior/middle temporal cortex, and lateral frontal cortex by several white matter pathways [21]. The perisylvian neural network is important for the

neural transformation of converging vestibular, auditory, neck proprioceptive, and visual input into egocentric spatial representations [22]. In healthy individuals, L-GVS induces activation of the perisylvian cortices in both hemispheres, whereas R-GVS induces only in the right hemisphere [23]. Although the mechanism by which GVS activates the same postulated brain areas in the lesioned brain as those found in healthy subjects is as

yet unclear, we suspect that the left hemisphere might compensate for the USN during L-GVS in patients with extensive dysfunction of the perisylvian network due to a subcortical lesion, as L-GVS produces a more widespread brain activation than R-GVS [22]. Thus, differences in the lesions of the present study's USN patients might have affected the results, and it is necessary to examine the differences in the effect of GVS on USN by lesion location. Furthermore, to our knowledge, there has been no study on the effects of repeated sessions of L-GVS on USN, and further studies with larger sample sizes should be conducted to determine the effectiveness of repeated sessions of L-GVS on USN.

The limitations of this study are as follows. First, the line cancellation test showed a ceiling effect. In particular, patient 7 achieved a perfect score on the line cancellation test before both L-GVS and R-GVS. Second, the examiners who evaluated the effects of GVS were not blinded to the treatments, which may have influenced the results. A third limitation is the small sample size. Small sample sizes are common in studies on the effect of GVS on USN due to the novel and explorative aspect of GVS research. We applied multiple stimulation conditions for the same patients, but there may not have been effects of the other stimulation conditions.

## Conclusion

In summary, 20 min of L-GVS increased the line cancellation test scores of USN patients more effectively compared with 10 min L-GVS and the other stimulus conditions we tested. There was a significant positive correlation between the amount of change in the line cancellation score with L-GVS and the total charge. Despite limitations, these results suggest that the effects of GVS on USN probably depend on the application duration, the current intensity, and the polarity, and a higher current intensity and longer application duration of L-GVS may increase the beneficial effect of GVS on USN. We consider that our present findings will help improve GVS treatment for USN.

## Acknowledgements

The authors thank Kentaro Tokuhisa for valuable suggestions and constant encouragement throughout the study.

## Conflicts of interest

There are no conflicts of interest.

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