The effect of repeated sessions of galvanic vestibular stimulation on target cancellation in visuo-spatial neglect:

Preliminary evidence from two cases

Abstract

Objective: In recent years it has emerged that the attentional disorder of visuo-spatial neglect can be overcome via artificial stimulation of the balance system. One means of achieving this is via galvanic vestibular stimulation (GVS), a simple procedure in which tiny, electrical currents are discharged to the part of the scalp overlying the vestibular nerves. Attempts to remediate neglect with GVS have utilised only a single session of stimulation, and although this can induce spontaneous recovery, symptoms resurface soon after stimulation. Here we assessed whether repeated sessions induce longer carry-over.

Methods: Two individuals diagnosed with neglect post-stroke received five days of sub-sensory, left anodal GVS. Performance was assessed via the letter and star cancellation tasks of the Behavioural Inattention Test on four occasions; three days before the start of stimulation, on the first and last day of stimulation, and three-days after stimulation.

Results: Analyses of variance indicated that both participants missed significantly fewer targets in both tasks on the fifth day of stimulation compared to baseline. More so, this improvement was still evident at follow-up three days later.

Conclusion: The results strengthen the need for a larger, sham-controlled trial to establish whether repeated GVS provides lasting relief from neglect.

Introduction

Visuo-spatial neglect is a disabling, neurological condition commonly acquired through stroke, and is characterised by an impaired ability to respond to visual stimuli presented in contralesional space. The condition most frequently occurs following a lesion to the right hemisphere, inducing a tendency to collide with left-sided objects and ignore people who approach from the left [1]. Neglect is a poor prognostic indicator of general functional recovery after stroke, extending length of hospital stay [2], and impacting functional independence post-discharge [3]. Although relatively common in right hemisphere stroke, the condition persists in approximately 20% of stroke survivors [4]. Unfortunately, the most widely practiced treatment for neglect, visual scanning therapy, is of limited efficacy [5]. More promising treatments are, however, beginning to emerge (see [6]), one of which is galvanic vestibular stimulation (GVS).

GVS modulates the firing rates of the vestibular nerves via the delivery of small-amplitude current (~1mA-2mA) to the overlying mastoid processes [7]. The brain interprets this modulation as a natural head movement, which in turn elicits a variety of cortical and subcortical compensatory responses. Neuroimaging indicates that GVS increases blood flow [8], and electrical power spectra [9] in those temporal-parietal and frontal regions of brain typically damaged in neglect. Such increases may be important for subsequent cognitive restoration and behavioural improvement [10]. At the psychological level, Karnath [11] has proposed that the central transformation that converts sensory input co-ordinates into an egocentric, body-centered co-ordinate system is systematically skewed in neglect, resulting in a horizontal deviation of the spatial reference frame to the ipsilesional side. The idea behind sensory stimulation is that by artificially boosting sensory inputs from the

neglected side, a correctional spatial bias is induced that runs counter to the rightward shift imposed by neglect [12]. That is, the existing spatial imbalance is eliminated by adding a new one of opposite magnitude.

Several research groups have shown that a single session of GVS can spontaneously reduce aspects of the neglect syndrome [13-15]. This observation builds on the longstanding finding that caloric vestibular stimulation, an allied method that modulates peripheral vestibular activity via thermal as opposed to electric waveforms but in a less controlled and tolerated manner, can produce dramatic and spontaneous relief from neglect [16,17]. A key drawback of vestibular stimulation is, however, that its effect on neglect seems to recede only minutes or hours after stimulation is withdrawn. To hold relevance to rehabilitative practice, the duration of carry-over must somehow be increased.

One clue to how longer carry-over might be achieved is apparent from the broader neuro-stimulation literature which indicates that persistent cognitive change tends to follow from repeated treatment sessions [18-20], a result that chimes with the idea that underlying neuro-plastic change relies on multiple stimulus exposures [21]. For example, Schindo and colleagues [18] showed that 6 daily sessions of transcranial magnetic stimulation (TMS) induced recovery from neglect that was still evident 6 weeks later. More widely, Kleinjung et al. [19] showed that 5 consecutive days of TMS led to a significant reduction of tinnitus for 6 months in 14 patients, while Naeser et al. [20] showed that 10 daily TMS sessions generated a 2 month improvement in picture naming in stable, chronic aphasic patients 3-6 months post-stroke. Although these findings give reason to explore the effects of long-term TMS in neglect patients, we should perhaps point out that GVS currently affords several advantages. Unlike TMS, GVS is delivered to a single, easily identifiable scalp

location (the mastoids), and relies on a small, battery-driven constant current generator that is lighter, portable and easier to operate by nurses and carers. Although strict safety protocols must be followed during GVS, these are less stringent and inclusive of more patient groups than those that accompany TMS [22]. As might be expected, the hardware needed to deliver TMS is relatively expensive, currently costing at least four or five times more than an off-the-shelf DC stimulator suitable for GVS. As a consequence, GVS may be a more viable tool for some developing healthcare economies.

In this small pilot study, we therefore assessed whether five consecutive daily sessions of GVS could induce an improvement in visual neglect that was still evident 3 days later. We chose a 3 day follow-up period because the aim was to simply show that it is possible to induce carry-over beyond just a few hours. If such carry-over could be shown then there would be reason to move ahead with a larger, properly controlled trial that more systematically investigated the effect of treatment repetition on carry-over. To assess change, we administered the letter and star cancellation tasks of the Behavioural Inattention Test (BIT) [23]. We chose these tests because they are highly sensitive to neglect [24], and because they emphasise the need for spatial exploration, an ability that runs to the heart of many daily activities.

Methods

Participant characteristics

Patient B.W, female, aged 61, suffered a right middle cerebral artery infarct (see figure 1a) 8 weeks prior to study enrolment and was still residing in hospital at the time of testing. On admission, she experienced severe left hemiparesis with no

active movement in her upper and lower left limbs, left facial palsy and dysphagia. The presence of left inattention was notable throughout administration of the NIH Stroke Scale [25] and although this was later shown to impact her reading and writing skills, no specific communication impairment was detected by the speech and language therapist. Pain sensation was normal, but touch, temperature and position sense were reduced. During eligibility screening, she scored 48/146 (normative cut-off = 129) on the conventional tests of the BIT, and often failed to respond when addressed from the left during daily ward routine. At the time of screening, muscle tone was increased in her left upper and lower limbs. Her MRC muscle power score was 0/5 in her left arm and 4/5 in her left leg. Upper and lower limb reflexes were especially brisk on the left side. A few days prior she scored 10 for anxiety and 10 for depression on the Hospital Anxiety and Depression Scale [26], suggestive of a mild mood disorder.

Patient S.M, male, aged 59, presented at admission with evidence of a right middle cerebral artery infarct with midline shift (see figure 1b) and underwent an emergency decompressive craniotomy. He showed a dense left hemiplegia and suffered a loss of sensation throughout his left side. Administration of the NIH Stroke Scale confirmed a florid, left-sided, personal and peri-personal neglect, which in turn impacted sitting balance and posture. Formal perimetry conducted shortly after revealed a left, homonymous hemianopia, although this was not reassessed at the time of study enrolment. No communication or swallowing difficulties were observed by the speech and language therapist. At the time of study enrolment, 38 months post-onset, S.M. was living semi-independently at home and scored 79/146 on the conventional tests of the BIT. He also produced an MRC muscle power score of 0/5

in his left arm and 4/5 in his left leg, and showed continued evidence of a mild, upper motor neuron-type left facial weakness.

Figure 1 about here

Behavioural Protocol

Both participants performed the letter and star cancellation sub-tests of the BIT on 4 separate occasions: 3 days before stimulation, on the first and last day of stimulation, and then 3 days later. During administration, the test sheets were placed in front of the participant on a desk, and aligned with the mid-sagittal plane. The experimenter sat directly opposite. On those days when stimulation was administered, participants performed the tests during (as opposed to after GVS). Both participants gave written informed consent prior to study commencement, and remained in good humour throughout. The study was approved by an NHS Research Ethics committee and conducted in accordance with the 1964 Declaration of Helsinki.

Stimulation Protocol

GVS was administered by applying bipolar current through a pair of 5.1cm x 10.2cm carbon-rubber, self-adhesive electrodes, placed over the mastoid processes. To ensure complete electrical contact with the electrodes, the skin surrounding the mastoids was cleansed with an alcohol wipe and conductive gel was coated on the underside of the electrodes. The anode was placed over the left mastoid and the cathode over the right mastoid. The electrodes were connected to a Magstim Eldith Transcranial DC Stimulator Plus™ device which discharged current at 90% of cutaneous sensory threshold (1mA for participant S.M and 1.5mA for participant

B.W.) for a period of 20 minutes on each of the 5 consecutive days. (Sensory threshold was determined prior to the baseline session using the staircase procedure described by Wilkinson et al. [27]). Participants were subsequently encouraged to report any unusual sensation such as itching/tingling behind the ears, but neither did. The participants wore the electrodes in the baseline but not follow-up session.

Results

The number of missed targets in the letter and star cancellation tasks were analysed separately for each participant using one-way ANOVAs (Session: Pre-GVS, GVS-1, GVS-5, Post-GVS). Post hoc pairwise comparisons were performed using the Tukey HSD test (α=0.05).

Participant B.W.

See figure 2a for a graph showing B.W.'s mean errors and figure 3 for reproductions of her cancellation performance.

Star cancellation: A one-way ANOVA revealed a significant effect of Session *($F(3, 215) = 8.4$, $p < 0.01$)*. Post hoc comparisons showed that B.W. missed fewer targets in the GVS-5 and post-GVS sessions compared to the pre-GVS session. Fewer targets were also missed in the GVS-5 and post-GVS sessions compared to the GVS-1 session. As can be seen from figure 2a, these reductions in the number of missed targets reflected a greater sensitivity to those appearing on the left-hand side, a pattern that is repeated in all datasets reported below. No other significant differences were found *($ps > 0.82$).*

Letter cancellation: A one-way ANOVA again revealed a main effect of Session (*F(3, 159) = 49.1, p < 0.01).* Post hoc comparisons revealed that, as with the star cancellation, B.W. missed fewer letters in the GVS-5 and post-GVS sessions compared to the pre-GVS session. BW was also more accurate in the GVS-5 and post-GVS sessions compared to the GVS-1 sessions. No other effects were significant *(ps > 0.42)*.

Figures 2 and 3 about here

Participant S.M.

See figure 2b for a graph showing S.M.'s mean errors and figure 4 for reproductions of his cancellation performance.

Star cancellation: A one-way ANOVA showed the main effect of Session to be reliable *(F (3, 215) = 16.0, p < 0.01).* The Tukey HSD test indicated that S.M. missed significantly more targets in the pre-GVS session compared to all other sessions. S.M. also missed more targets in the first GVS session compared to the post-GVS session. No other differences were significant (*ps > 0.07*).

Letter cancellation: As with star cancellation, a one-way ANOVA indicated a significant main effect of Session *(F (3, 159) = 7.1, p < 0.01).* Post hoc comparisons showed that S.M. missed fewer targets in the GVS-5 and post-GVS sessions compared to the pre-GVS session. No other differences were significant (*ps > 0.2*).

Figure 4 about here

Discussion

Previous studies have shown that a single session of vestibular stimulation can improve performance on tests of unilateral neglect [13-15]. However, the duration of improvement has remained uncertain, either because it has not been measured or because it has fallen away after just a few hours. Here we wanted to establish whether it was possible to prolong carry-over to a period of days rather than hours. Given the general notion that lasting neuro-plastic change is most likely to occur following multiple stimulus exposures [21], we administered five daily sessions and then tested for carry-over 3 days later. Compared to the baseline, both neglect participants showed a significant improvement in their star and letter cancellation performance after 5 days of stimulation. Consistent with a cumulative effect, the level of improvement on the fifth day was generally greater than that seen on the first. Most important, the level of performance seen at day 5 was still apparent 3 days after stimulation was stopped. In the case of participant S.M., the number of targets missed at baseline had diminished by 37% at follow-up (37%-0%) for star cancellation and by 25% (30% to 5%) for letter cancellation. In the case of participant B.W., the number of targets missed at baseline had diminished by 35% at follow-up (85% to 50%) for star cancellation and by 70% (90% to 20%) for letter cancellation. These data are important because they indicate that GVS may be able to induce long-term relief from neglect. Given that neither participant showed ill-effect, these data also confirm our earlier report that 5 days of stimulation are well-tolerated [28].

On a cautionary note, we point out that that in the absence of a sham condition, it is not possible to discount the effects of natural recovery, practice and/or placebo. That said, participants wore the electrodes during the baseline session, so if there was a strong placebo effect then one might have expected little change from

baseline to actual stimulation (note that all stimulation was sub-sensory). Given that both participants, especially S.M., had showed a relatively stable neglect for weeks prior to testing, we are reluctant to believe that the sudden change in cancellation performance simply reflected natural recovery. Finally, cancellation tests have shown good test-retest reliability, especially in more severe cases of neglect such as those assessed here [29]. Although these considerations lend a degree of confidence to the current findings, a larger, properly controlled trial is now needed for both confirmatory purposes and to determine whether there is transfer to activities of daily living. For the time being, we wish to highlight the potential, albeit often underplayed, contribution of GVS to neglect rehabilitation.

Acknowledgements

We thank B.W. and S.M for their patient assistance throughout the study.

Declaration of Interest

The authors report no declarations of interest.

References

1. Robertson I, Halligan P. Spatial neglect: A clinical handbook for diagnosis and treatment. Hove: Psychology Press; 1999.
2. Wilkinson D, Sakel M, Camp SJ, Hammond L. Patients with hemispatial neglect are more prone to limb spasticity, but this does not prolong their hospital stay. Archives of Physical Medicine and Rehabilitation 2012; 93:1191-5.
3. Katz N, Hartman-Maeir A, Ring H, Soroker N. Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. Archives of Physical Medicine and Rehabilitation 1999;80:379-84.
4. Ringman J, Saver J, Woolson R, Clarke W, Adams H. Frequency, risk factors, anatomy and course of unilateral neglect in an acute stroke cohort. Neurology 2004;10:468-74.
5. Bowen A, Lincoln N. Cognitive Rehabilitation for spatial neglect following stroke. Cocherane Database of Systematic Reviews 2007; 2:No.CD003586.
6. Kerkhoff G, Schenk T. Rehabilitation of neglect: an update. Neuropsychologia 2012;50:1072-9.
7. Coats AC. Limit of normal of the galvanic body-sway test. The Annals of Otology, Rhinology and Laryngology 1972;81:410-416.
8. Bense S, Thomas S, Yousry T, Brandt T, Dieterich M. Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). Journal of Neurophysiology 2001;85:886-899.

9. Wilkinson D, Ferguson H, Worley A. Galvanic vestibular stimulation modulates the electrophysiological response during face processing. Visual Neuroscience 2012;15:1-8.
10. Mori S, Sadoshima S, Ibayashi S, Lino K, Fujishima M. Relation of cerebral blood flow to motor and cognitive functions in chronic stroke patients. Stroke 1994;25:309-17.
11. Karnath HO. Disturbed coordinate transformation in the neural representation of space as the crucial mechanism leading to neglect. In: Halligan PW, Marshall JC, editors. Spatial-neglect: position papers on theory and practice. Hillsdale, NJ: Lawrence Erlbaum; 1994.
12. Kerkhoff G. Modulation and rehabilitation of spatial neglect by sensory stimulation. Progress in Brain Research 2003;142:257-71
13. Rorsman I, Magnusson M, Johansson BB. Reduction of visuo-spatial neglect with vestibular galvanic stimulation. Scandinavian Journal of Rehabilitation Medicine 1999;31:117-24.
14. Saj A, Honoré J, Rosseaux M. Perception of the vertical in patients with right hemispheric lesion: effect of galvanic vestibular stimulation. Neuropsychologia 2006; 44:1509-12.
15. Utz K, Keller I, Kardinal M, Kerkhoff G. Galvanic vestibular stimulation reduces the pathological rightward line bisection error in neglect – a sham stimulation-controlled study. Neuropsychologia 2011;49:1219-25.
16. Cappa S, Sterzi R, Vallar G, Bisiach E. Remission of hemineglect and anosognosia during vestibular stimulation. Neuropsychologia 1987;25:775-82.
17. Rubens A. Caloric stimulation and unilateral neglect. Neurology 1985;35: 1019-24.

18. Shindo K, Suglyama K, Huabao L, Nishijima K, Kondo T, Izumi S. Long-term effect of low frequency repetitive transcranial magnetic stimulation over the unaffected posterior parietal cortex in patients with unilateral spatial neglect. Journal of Rehabilitative Medicine 2006;38:65-7.
19. Kleinjung T, Eichhammer P, Langguth B, Jacob P, Marienhngen J, Hajak G, Wolf S, Strutz J. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolayrngology, Head and Neck Surgery 2005;132: 566-9.
20. Naeser M, Martin P, Ho M, Treglia E, Kaplan E, Bashir S, Pascual-Leone A. Transcranial magnetic stimulation and aphasia rehabilitation. Archives of Physical Medicine and Rehabilitation 2012;93:S26-34.
21. Hoffman R, Cavus I. Slow transcranial magnetic stimulation, long-term depotentiation and brain hyperexcitability disorders. American Journal of Psychiatry 2002;159:1093-102
22. Utz K, Dimova V, Oppenländer K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology--a review of current data and future implications. Neuropsychologia 2010;48:2789-810.
23. Halligan P, Wilson B, Cockburn J. A short screening test for visual neglect in stroke patients. International Disability Studies 1987;12:95-9.
24. Halligan P, Marshall J, Wade D. Visuo-spatial neglect: underlying factors and test sensitivity. Lancet 1989;Oct:908-11.
25. Brott T, Adams H, Olringer C, Marler J, Barsan W, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, Rorick M, Moomaw V, Walker M. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20:864-70.

26. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica 1983; 67:361-370.
27. Wilkinson D, Nicholls S, Pattenden C, Kilduff P, Milberg W. Galvanic vestibular stimulation speeds visual memory recall. Experimental Brain Research 2008;189:243-8.
28. Wilkinson D, Zubko O, Sakel M. Safety of repeated sessions of galvanic vestibular stimulation following stroke: a single-case study. Brain Injury 2009; 10:841-5.
29. Bailey M, Riddoch M, Crome P. Test-retest stability of three tests for unilateral neglect in patients with stroke: star cancellation, line bisection and the baking tray test. Neuropsychological Rehabilitation 2004;14:403-19.

Figure Captions

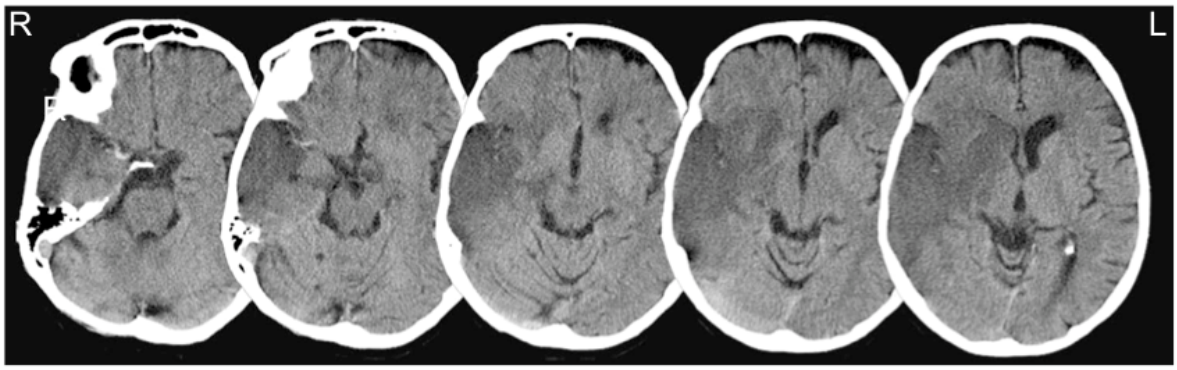
Figure 1. Participant CT Scans. (a) Selected axial sections of Participant B.W.'s brain lesion, showing a large ill-defined wedge shaped area of low attenuation within the right frontal, parietal, and temporal lobes with deep white matter extension into the ipsilateral basal ganglia. The right middle cerebral artery is hyperdense compared to the contralateral side in keeping with the 'dense artery sign' of an acute MCA thrombus. There is sulcal effacement and loss of normal gyral patterns. A mass effect partially effaces the right ventricle with an anterior horn predominance, causing a midline shift of 6mm. (b) Selected sections of Participant S.M.'s brain lesion, showing gliosis and porencephaly in the right middle cerebral artery territory including all of its segments, with dilatation of the ipsilateral ventricle. There is also evidence of a small, hyperdense extra axial collection with a maximum depth of 8.5mm, consistent with a subdural haemotoma following craniotomy.

Figure 2. Percentage of targets omitted in the star and cancellation tasks for Participants (a) B.W. and (b) S.M.

Figure 3. Spatial distribution of target omissions produced by Participant B.W. Missed targets are highlighted via either a circle (in the star cancellation task) or rectangle (in the letter cancellation task).

Figure 4 Spatial distribution of target omissions produced by Participant S.M. Missed targets are highlighted via either a circle (star cancellation task) or rectangle (letter cancellation task).

(a)



(b)

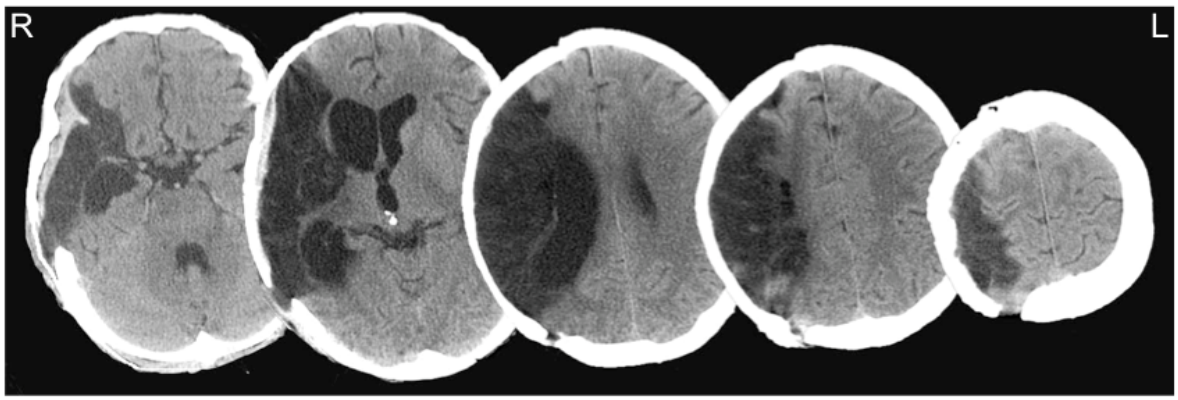
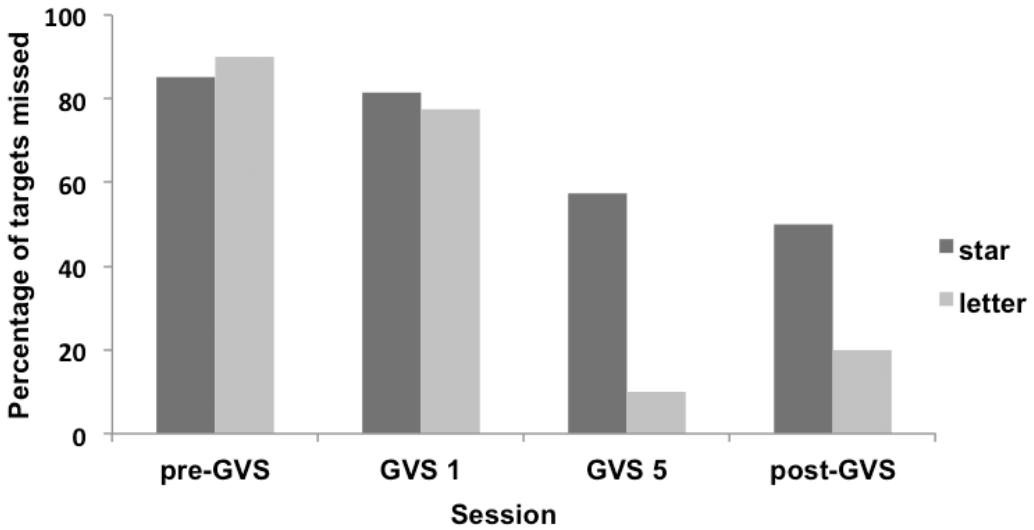


Figure 1

(a)


Percentage of targets missed
100
80
60
40
20
0
pre-GVS
GVS 1
GVS 5
post-GVS
Session
star
letter

(b)

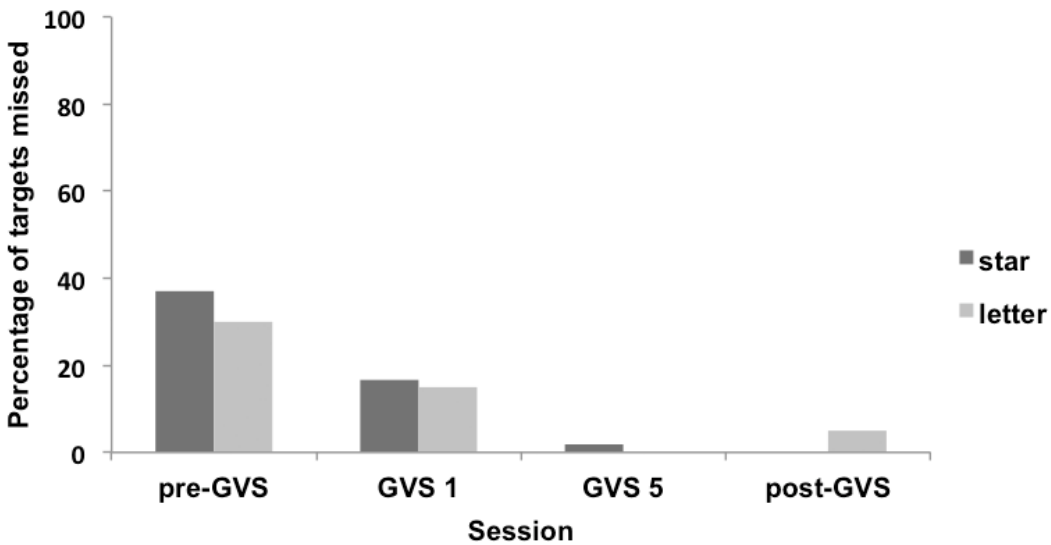
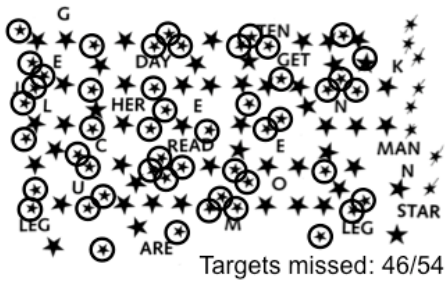
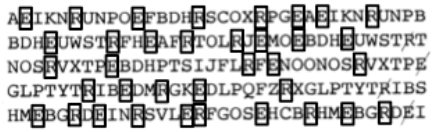

Percentage of targets missed
100
80
60
40
20
0
pre-GVS
GVS 1
GVS 5
post-GVS
Session
star
letter

Figure 2

Pre-GVS

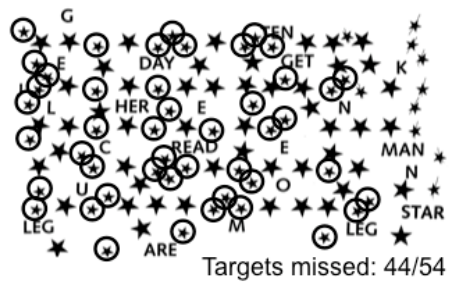


Targets missed: 46/54



Targets missed: 36/40

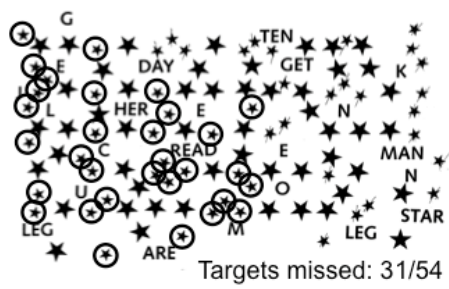
GVS-1



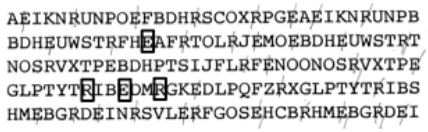
Targets missed: 44/54

Targets missed: 31/40

GVS-5

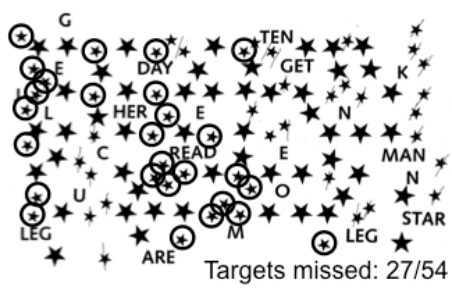


Targets missed: 31/54

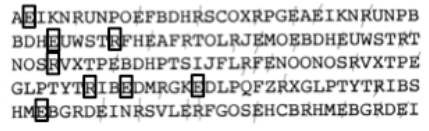


Targets missed: 4/40

Post-GVS



Targets missed: 27/54

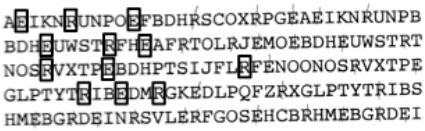


Targets missed: 8/40

Figure 3

Pre-GVS

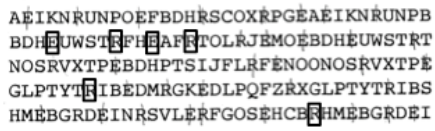
Targets missed: 20/54



Targets missed: 12/40

GVS-1

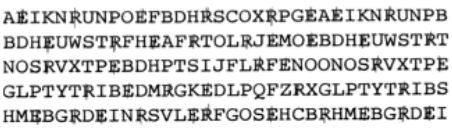
Targets missed: 9/54



Targets missed: 6/40

GVS-5

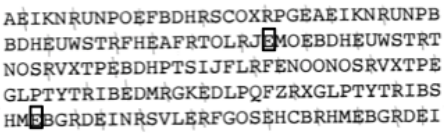
Targets missed: 1/54



Targets missed: 0/40

Post-GVS

Targets missed: 0/54



Targets missed: 2/40

Figure 4