Spatial neglect after stroke is reduced when lying inside a 3T MRI scanner

Hans-Otto Karnath[1,3]*†, Hannah Rosenzopf[1], Stefan Smaczny[1], Axel Lindner[1,2]*†

[1] Center of Neurology, Division of Neuropsychology, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

[2] Tübingen Center for Mental Health, Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

[3] Department of Psychology, University of South Carolina, Columbia, SC 29208, USA

* These authors contributed equally to the paper.

† Shared Correspondence (karnath@uni-tuebingen.de; a.lindner@medizin.uni-tuebingen.de).

Addresses for correspondence:

Hans-Otto Karnath
Center of Neurology
University of Tübingen
Hoppe Seyler Str. 3
D-72076 Tübingen
Germany
e-mail: karnath@uni-tuebingen.de

Axel Lindner
Center of Neurology
University of Tübingen
Hoppe Seyler Str. 3
D-72076 Tübingen
Germany
a.lindner@medizin.uni-tuebingen.de

Abstract

Recently, it was discovered that the static magnetic field of an MRI scanner not only causes horizontal vestibular nystagmus in healthy individuals but, in addition, leads to a horizontal bias of spatial orienting and exploration that closely resembles the one observed in stroke patients with spatial neglect. The present study asked whether the behavioral effects of this magnetic vestibular stimulation (MVS) can be inverted and thus be used to reduce the pathological bias of stroke patients with spatial neglect. Indeed, when W.E., a patient with left-sided spatial neglect, entered the scanner with his feet first, i.e., with the magnetic field vector pointing from his head to the toes, MVS inside the scanner reduced the ipsilesionally biased distribution of overt attention and the corresponding neglect of the left parts of the search-space. Thus, an intervention as simple as lying in a 3T MRI scanner bears the potential to become an integral part of a future strategy for treating spatial neglect.

Key words

Magneto-hydrodynamic vestibular stimulation; MVS; fMRI; spatial neglect; stroke; human; vestibular ocular reflex; VOR; spatial stability; eye movements

Introduction

While the widespread use of magnetic resonance imaging in the clinical and scientific fields emerged in the 1980s, it has been reported only recently that healthy subjects exposed to the static magnetic fields of MRI scanners exhibit a persistent horizontal vestibular nystagmus. Since this effect's initial description by Marcelli and co-workers (2009) and subsequent systematic investigation by Roberts and colleagues (2011), several studies have replicated this effect and confirmed the hypothesis that the stimulation of the vestibular organ is induced by Lorentz forces resulting from the interaction of the MR scanner's static magnetic field with ionic currents in the endolymph fluid of the subject's labyrinth (see Ward et al., 2019 for review). Only recently, Lindner and co-workers (2021) found that the MR static magnetic field not only causes horizontal vestibular nystagmus in healthy individuals but in addition leads to a horizontal bias of spatial orienting and exploration that closely resembles that seen in stroke patients with spatial neglect.

Spatial neglect is a visuo-spatial attention disorder occurring after stroke, most typically of the right hemisphere. Patients with spatial neglect show spontaneous and sustained deviation of their eyes and head (Fruhmann-Berger & Karnath 2005) as well as focus of attention towards the ipsilesional, right side of space (Heilman et al., 1983; Karnath & Rorden, 2012; Karnath, 2015). When the eye movements of such patients are recorded during visual search, an asymmetric, spatially biased exploratory behavior becomes visible (Karnath et al., 1998), leading to neglect of the contralesional side of the surrounding scene.

The present study was motivated by the aforementioned observation that magnetic vestibular stimulation (MVS) by lying inside a 3T MRI scanner induces spatial biases in healthy subjects that mimic those observed in neglect patients (Lindner et al., 2021). In the main experiment by Lindner and colleagues, the subjects lay in the scanner in the conventional neurological position, namely entering the scanner with their heads first, resulting in the magnetic field vector of our scanner pointing from subjects' toes to their heads. Under this condition, the center of healthy subjects' visual scan-path during visual search deviated towards the right, as is also the case for most patients with spatial neglect (compare above). Lindner et al. (2021) further observed that for an "inverted" positioning in the scanner, i.e., when subjects entered the scanner with their feet first, MVS led to inverted behavioral effects: healthy subjects now showed a bias to the left instead of to the right side. We thus asked whether the behavioral effects of MVS on spatial attention and orientation during "inverse positioning" could be used to reduce the pathological core symptoms of stroke patients with spatial neglect of the left side of space. Hence, in the current study, we examined whether an inverted MVS-effect would directly counteract the pathological bias of neglect patients.

Methods

Neglect patient W.E.

Patient W.E. is a 64-year-old right-handed male patient who suffered a stroke 7 days before the present experimental investigation. W.E was admitted to our department after having developed left-sided hemiparesis and dysarthria. The initial CT perfusion and CT angiography uncovered a fronto-laterally located perfusion deficit and occlusion of the M2 segment of the middle cerebral artery in the right hemisphere. Lysis therapy was initiated but aborted when the patient indicated it could have been a wake-up stroke (after he had originally documented that symptoms had started while being awake). A magnetic resonance T2 fluid attenuated inversion recovery (FLAIR) sequence one day after admission uncovered a timely demarcation in the territory of the right middle cerebral artery (Fig. 1).

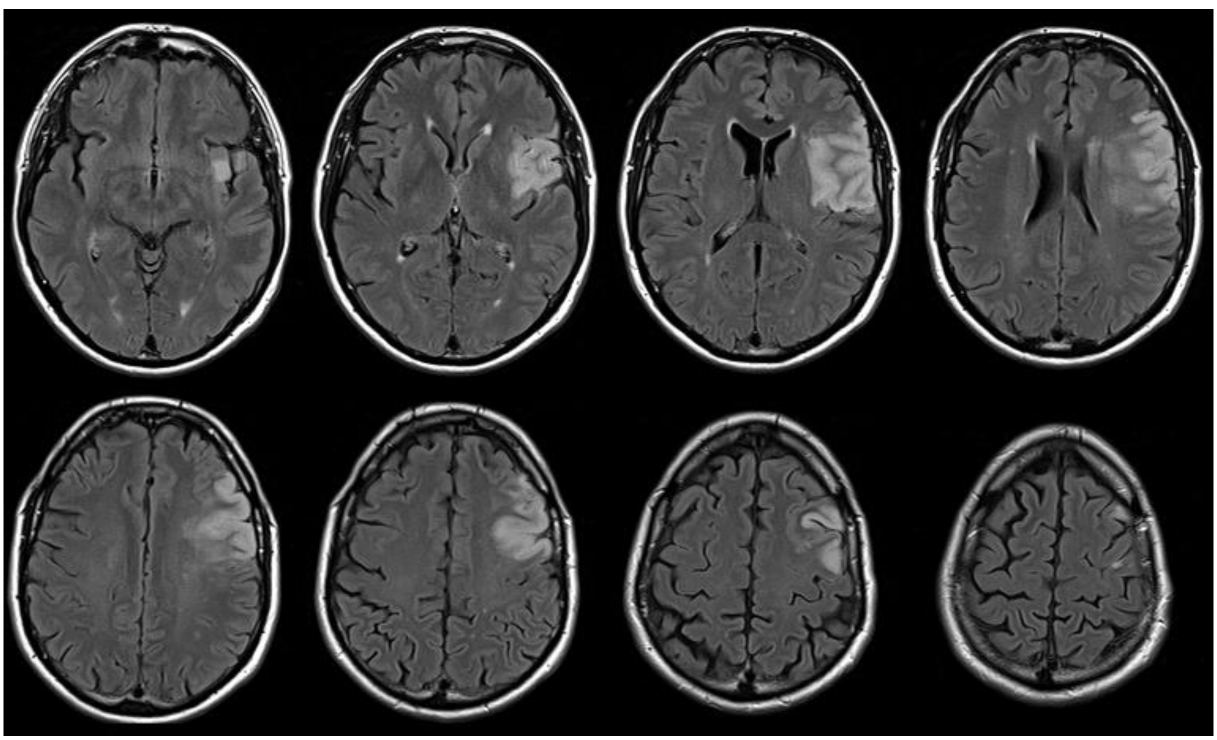

Fig. 1. T2-weighted FLAIR magnetic resonance image of patient W.E. performed one day after stroke-onset.

Neuropsychological examination included the following four tests of spatial neglect: the Letter Cancellation Test (Weintraub & Mesulam, 1987), the Bells Test (Gauthier et al., 1989), a Copying Task (Johannsen & Karnath, 2004), and a Line Bisection Task (following the procedure described by McIntosh et al. [2005]). All four neglect tests were performed on a Samsung S7+ tablet with screen dimensions 285x185mm. The severity of spatial neglect in the cancellation tasks was determined by calculating the center of gravity of the target stimuli marked in the search fields, i.e. the Center of Cancellation (CoC; Rorden & Karnath, 2010). A CoC value ≥ 0.08 indicated left-sided spatial neglect (Rorden & Karnath, 2010). The Copying Task consisted of a complex scene consisting of four objects (fence, car, house, tree), points were assigned based on missing details or whole objects. One point was given for a missing detail, two for a whole object. The maximum number of points is therefore 8. A score higher than 1 (i.e. > 12.5% omissions) indicated neglect (Johannsen & Karnath, 2004). In the Line Bisection Task, patients were presented four different line lengths eight times each, i.e., 32 lines in total (McIntosh et al., 2005). The cut-off value for spatial neglect was an endpoint weightings bias (EWB) value ≥ 0.07 (McIntosh et al., 2017).

In the diagnostic procedure 4 days post-stroke, W.E. obtained results indicating spatial neglect in two of the diagnostical tests. He omitted targets towards the left end of the Bells cancellation test (Fig. 2), which resulted in a pathological CoC score of 0.163, and he omitted the leftmost object when asked to copy a multi-object scene (Fig. 2), resulting in a Copying-Task score of 2. The line bisection test could not be scored, because the patient did not follow instructions but drew circles on the lines instead. The letter cancellation test showed a CoC score of - 0.021.

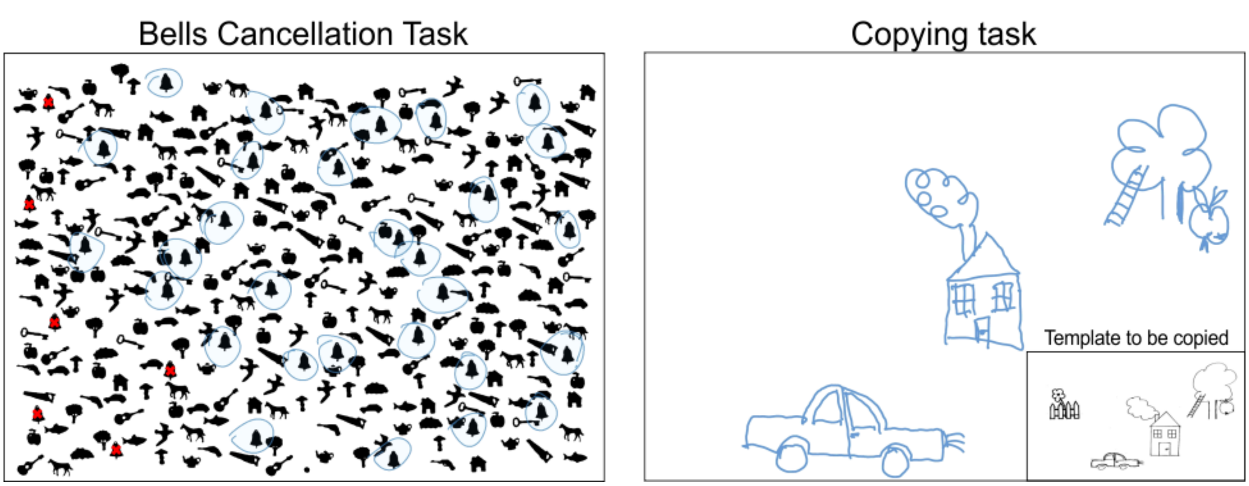

Fig. 2. W.E. omitted the leftmost targets in the Bells Cancellation Task (left; red crosses were added afterwards to highlight W.E.'s omissions) and the leftmost object (=fence) in the Copying Task (right).

Control group

The control group consisted of a sample of six healthy subjects (1 male and 5 females; average age 26.3±3.4 years SD). All subjects reported to be right-handed, had normal or corrected to normal vision, and reported no vestibular or neurological deficit. These subjects have also been included in a previous study (Linder et al., 2021). All subjects, including W.E., provided their informed consent according to our institutional ethics board guidelines prior to our experiment.

MRI Setting

We used a 3T Siemens MAGNETOM Prisma MRI Scanner to apply MVS. No radio frequency (RF) or gradient coil fields were applied. Contrary to the standard subject positioning in neurology/neuroscience, patient W.E. and controls entered the scanner with the feet first (Fig. 3b). Therefore, the magnetic field vector of our MRI system pointed from subject's head to the toes. To this end a 20-channel head coil (Siemens Head/Neck 20 A 3T Tim Coil) was placed at the feet-end of the scanner table. We tried to maximize the effects of MVS on the horizontal canals by positioning subjects with their heads tilted -30° backwards inside the head-coil (canthus-tragus-line vs. vertical; cf. Roberts et al., 2011; Boegle et al., 2016). Cushions were used to stabilize head position and prevent head movements. A mirror was mounted on top of the head-coil to provide subjects with an indirect view on our custom-made black visual search-screen. The screen was placed behind the coil on the scanner table at about 110 cm viewing distance. Various glass-fiber-cables penetrated the screen at discrete locations and allowed the presentation of small visual stimuli by feeding these cables with LED light signals. Maximal target distance from the screen center amounted to ±12° visual angle in the horizontal direction and to -5° to 6° in the vertical direction. An IR-video-camera unit was mounted next to the mirror to record a video-signal of subjects' right eye. The study was conducted in complete darkness by extinguishing all light sources and covering subjects with a black blanket (cf. Fig. 3a). This was important, as any visible stimulus that would be present in the subjects' visual field could help them to suppress an MVS-induced VOR as well as to explore the visual scene and to perform the SSA task in an unbiased fashion.

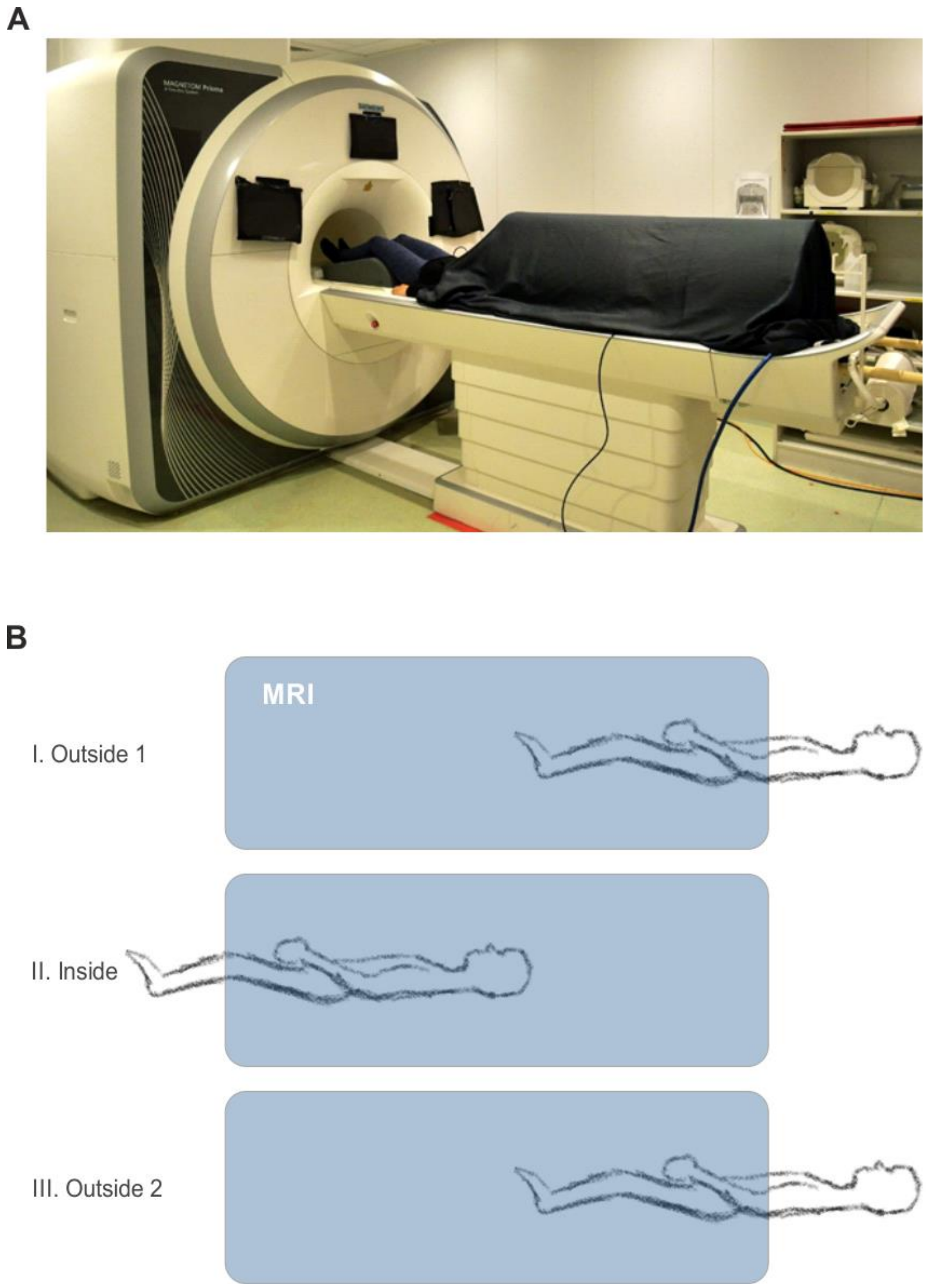

Fig. 3. Experimental setting and procedure. **A** Contrary to the standard subject positioning in neurology/neuroscience, neglect patient W.E. and controls entered the scanner with the feet first. Subjects were covered with a black blanket extinguishing all light sources. **B** Three consecutive conditions were performed: I. measuring outside the scanner with the patient's head at its maximal horizontal displacement from the scanner center ("*outside 1*"), II. measuring inside the scanner where the strength of the uniform magnetic field is 3 Tesla ("*inside*"), followed by III. measuring outside the scanner again ("*outside 2*").

Stimulus Generation

A WIN10 laptop PC was used to control our experiment through custom scripts using MATLAB R2015b 32bit (MathWorks) in combination with Cogent 2000 and Cogent Graphics (by FIL, ICN, LON at the Wellcome Department of Imaging Neuroscience, University College London) as well as with the MATLAB Support Package for Arduino. Light stimuli were generated through 8 red LEDs (Type: L-513HD; Dropping resistor: 58kΩ) using an Arduino UNO R3-compatible microcontroller (Funduino UNO R3) that was controlled by MATLAB. The intensity of six of those LEDs could be adjusted using the Arduino's pulse code modulated (PCM) analog voltage output (0V-5V). The remainder of the LEDs could only be switched on/off (0V or 5V). This way we were able to deliver dim light stimuli through the fiber-ends inside the scanner. During the visual search task (see below) the voltage of the 6 search target LEDs was PCM-modulated across the 5 seconds presentation time for a given target, starting with 0.1V while doubling voltage in 1 second steps up to 1.6V. Through this manipulation we slowly increased the visibility of the search targets to increase the likelihood that patient W.E. as well as controls would find them. Apart from these transient light stimuli, subjects remained in complete darkness. The six search targets were at the following x/y–locations (values denote visual angle; positive values represent rightward/upward directions, respectively): -6°/5°; 6°/5°; -6°/-5°; 6°/-5°; -12°/-1°; 12°/1°. The final central search target was always at 0°/0°. Finally, the following 5 targets served for eye-calibration: 0°,0°; -6°/5°; 6°/5°; -6°/-5°; 6°/-5°.

Eye Tracking

The position of subjects' right eye was monitored at 50 Hz sampling rate with an MR-compatible camera with integrated infrared LED illumination (MRC Systems; Model: 12M-i IR-LED). We used the ViewPoint Monocular Integrator System and the View Point Software (Arrington Research, software version 2.8.3.437) to digitize the eye-camera video and to obtain uncalibrated eye-position data (by means of dark pupil tracking). Eye-tracking was realized on a different WIN PC that was remote-controlled through the ViewPoint Ethernet-Client running on our laptop PC. Eye movement analyses were performed off-line using custom routines written in MATLAB R2017b (MathWorks). Details are given in Lindner et al. (2021).

Time course of experiment

The procedure of the experiment is illustrated in Figure 3b. Three consecutive conditions were performed: measuring outside the scanner (*outside 1* phase) with the patient's head at its maximal horizontal displacement from the scanner center (head coil at ~ 215cm/0cm horizontal/vertical displacement)*;* the strength of the magnetic field in this position is roughly 50 times smaller than at the scanner center (head coil at ~ 10 cm/0cm horizontal/vertical displacement). Subsequently, we measured inside the scanner (*inside* phase) where the strength of the uniform magnetic field is 3 Tesla, followed by again measuring outside the scanner (*outside 2* phase). Each of the three phases started with an initial calibration for eye-tracking (see above). Next, we performed a nystagmus measurement. For this measurement, subjects were instructed to fixate at a dim light-point presented in the center of their visual field for 5 seconds. Then the dim light-point was switched off and subjects were asked to try maintaining central fixation for 60 seconds in otherwise complete darkness. This task was used to quantify subjects' horizontal VOR during an instructed fixation. Finally, subjects performed a "*visual search task*". During this task, patient W.E. and controls were asked to find and fixate transient light stimuli. In addition, we asked them to press a button on an MRI-compatible response pad (5-Button Diamond Response Pad; Current Designs) whenever they found a search target. We presented 6 search targets (each slowly fading-in over a period of 5 seconds). Locations of search targets were pseudorandomized across the three phases. The presentation of these stimuli only served to maintain the subjects' motivation to search for possible targets throughout the search period. Thus, for most of the time (i.e., 140 seconds; total duration of visual search task: 172 seconds), no visible target was present and the subjects were searching in complete darkness. For data analysis we discarded the time periods with targets present (plus an additional grace period of 5 seconds after a light stimulus was turned off; this was done to prevent carry-over effects from prior target-fixation). The search task always ended with a central light stimulus presented during the last 2 seconds (also not considered for data analysis). Subjects' heads were in the center of the MRI-scanner for approximately 10 minutes. For the *outside 2* phase, we ensured that our experimental measures were only obtained after patient W.E. and controls had left the MRI-scanner for approximately 3 minutes in order to account for putative MVS-aftereffects (Jareonsettasin et al., 2016).

Statistical Analyses

The statistical procedures to test for any MVS-effects on the behavior of our group of healthy control subjects have been described in detail before (Lindner et al., 2021). In order to probe for comparable

MVS-induced effects on patient W.E.'s horizontal VOR as well as on his horizontal center of visual search, we took individual samples of de-saccaded horizontal eye velocity and horizontal saccade endpoints of the respective experimental phases as measures. Since these latter data were not normally distributed (Shapiro-Wilk-Test; $p<0.01$), we performed Wilcoxon rank sum tests (two-tailed tests: *outside 1* vs. *inside* and *outside 2* vs. *inside*).

To compare patient W.E.'s behavior to that of the control group, we performed the following single-case statistics: First, for each experimental phase we probed whether patient W.E.'s VOR and his visual search would be different from the control group. To do this we applied the SINGLIMS-tests (Crawford & Garthwaite, 2002; Crawford & Howell, 1998). In the case of the data from the "*visual search task*", we performed a one-tailed test, as we expected a specific bias towards the right (as is typical for spatial neglect patients; cf. Karnath et al., 1996, 1998), Second, we investigated whether the *relative changes of these measures* from *outside 1* to *inside* and from *inside* to *outside 2* would be numerically different in W.E. as compared to our control group. This was tested by means of the two-tailed revised standardized difference tests (RSDT; Crawford & Garthwaite, 2005). All respective p-values of the SINGLIMS and RSDT tests were Bonferroni-corrected for multiple testing within each measure of interest.

Results

Figure 4 illustrates the resulting eye-data of patient W.E. throughout all tasks and phases. During the *inside* phase we observed the typical saw-tooth-like eye movement pattern, which is characteristic for a vestibular nystagmus (Fig. 4a, left column). It consisted of a slow leftward VOR that was accompanied by fast resetting saccades in the opposite rightward direction. This prototypical nystagmus-pattern was largely reduced for the *outside 1&2* phases. The average slow eye velocity for the *outside 1* phase was -0.54°/s on average and decreased to -1.97°/s for the *inside* phase (Fig. 4a, middle column). After removing the patient from the scanner bore to *outside 2*, average slow eye velocity increased to -0.25°/s. Average horizontal eye velocity of patient W.E. was significantly smaller during *inside* as compared to *outside 1* and as compared to *outside 2*, respectively ($p<0.001$ each; Wilcoxon rank sum tests). Importantly, these changes in patient W.E.'s VOR were statistically indistinguishable from those of the healthy control group (two-tailed revised standardized difference tests: all $p>0.165$ [corrected]). Moreover, patient's VOR was also indistinguishable from that of control subjects in all task phases in isolation (SINGLIMS test: all $p>0.111$ [corrected]).

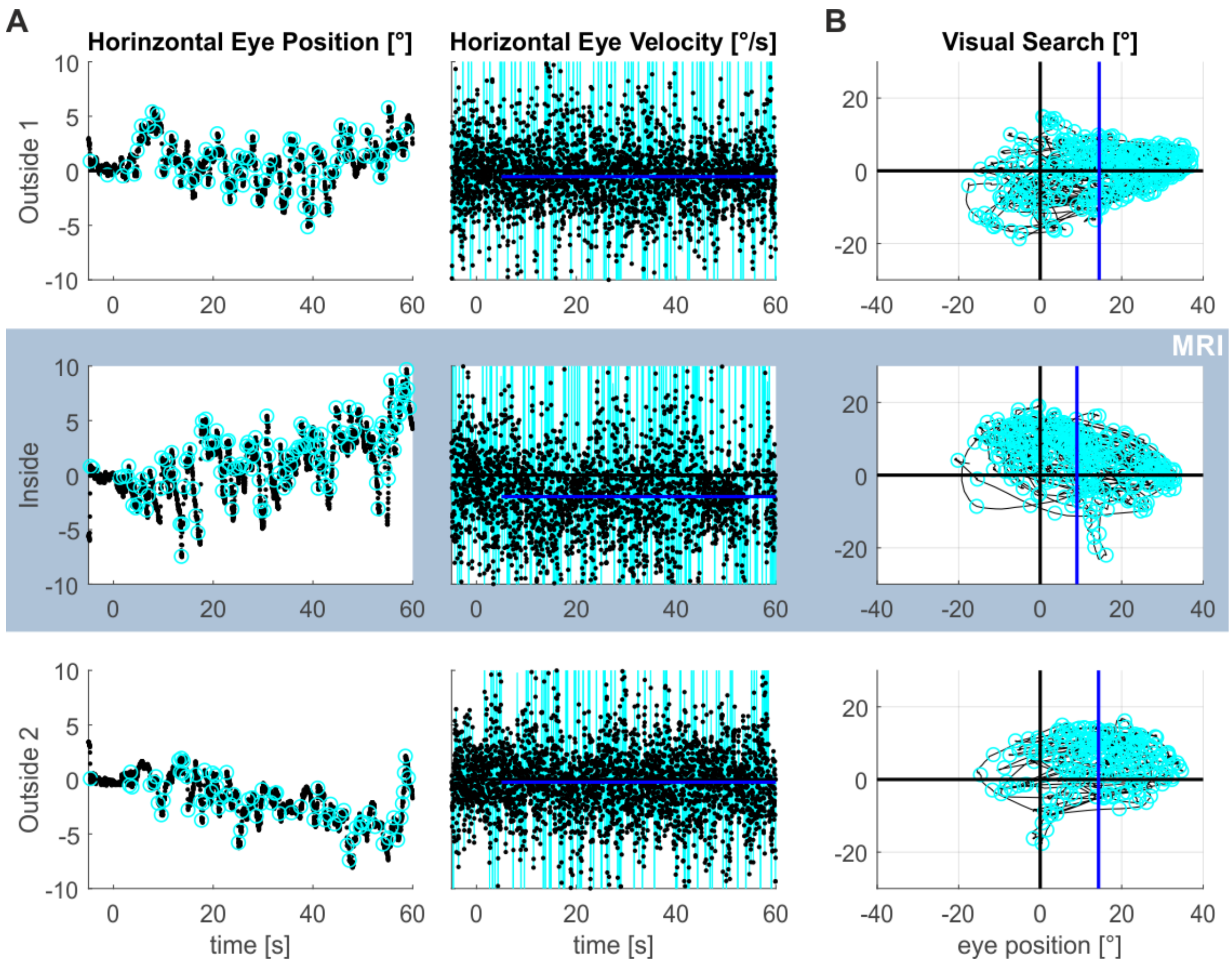

Fig. 4. MVS-induced oculomotor behavior in spatial neglect patient W.E. in the three phases (*outside 1*, *inside*, *outside 2*). **A** shows data from our nystagmus measurement. Horizontal eye position data are shown in the left column. Saccade endpoints are depicted by the cyan circles. Corresponding horizontal eye velocity traces are shown in the middle column. Note that the cyan peaks in these time-courses refer to individual saccades, which have been removed from the eye velocity records to allow estimation of slow-phase velocity in isolation (the blue lines indicate the respective horizontal VOR-estimates). **B** illustrates the 2D eye-position data from the visual search task (time periods with search targets plus 5 seconds were excluded). The horizontal center of visual search is depicted by the blue vertical lines, reflecting the mean of horizontal saccade endpoints (cyan circles). Positive values indicate the rightward/upward direction.

Figure 4b demonstrates a 2D-plot of the patient's eye position during search, including only those time epochs when no target stimulus was presented (cf. methods section). As was expected for patients with spatial neglect (Karnath et al., 1996, 1998), patient W.E. showed a biased ocular exploratory search pattern towards the ipsilesional right side during the *outside 1* phase (cf. Fig. 4b). The mean horizontal location of his visual search was biased +14.48° towards the right. In contrast, the control group showed a mean of 0.76° (3.28° SD; Fig. 5); i.e., they on average explored visual space more homogenously towards the left and right of their trunk midline. Statistical comparison of W.E. versus the control group revealed a significant difference (p=0.018 [corrected]; one-tailed SINGLIMS-test), indicating that patient W.E.'s visual search pattern during *outside 1* was indeed pathologically biased towards the right. The same was true during *outside 2*: patient W.E. showed the same rightward bias (14.32°), that was again statistically different from controls (mean 2.06° (2.05° SD), p=0.003 [corrected]; one-tailed SINGLIMS-test).

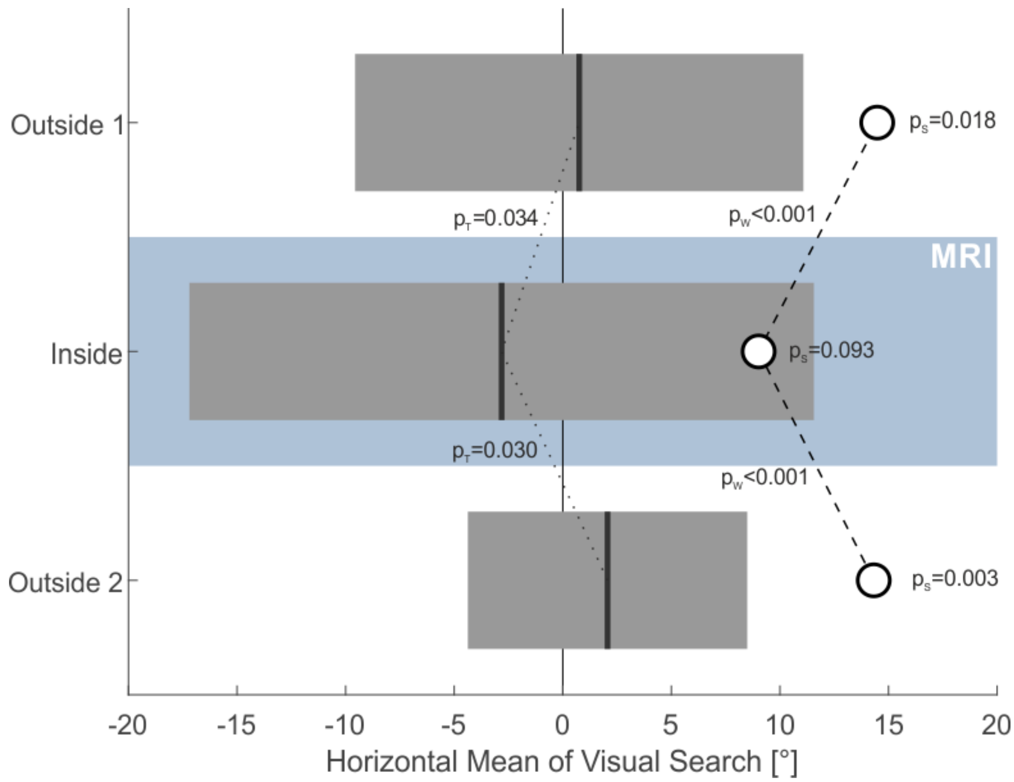

Fig. 5. MVS-induced leftward bias in visual search in patient W.E. and in healthy controls. The horizontal center of visual search of W.E. (white circles) and the respective means (black lines) of the control group (N=6) are shown for all three task phases. Positive values denote rightward biases. The grey boxes reflect the 95% confidence interval [corrected] of the difference between the normal population mean and the patient's score (SINGLIMS-test; respective p-values are provided as p_S [corrected for multiple comparisons]). Additional p-values are provided for the paired t-test comparisons of changes in control subjects' center of visual search across task phases (p_T; compare Lindner et al., 2021) as well as for the corresponding Wilcoxon rank sum tests in W.E. (p_W).

While the area of W.E.'s visual search for both *outside* phases was biased far towards the right, as is typical for spatial neglect (cf. Karnath et al., 1996, 1998), this pathological search bias was clearly reduced when patient W.E. was *inside* (9.02°). Statistical analysis revealed that his leftward-shift for *inside* was significantly different from both *outside1* and *outside 2* ($p<0.001$ each; Wilcoxon rank sum tests). The relative changes in patient W.E.'s visual search from *outside 1* to *inside* and from *inside* to *outside 2* were, however, indistinguishable from the respective relative changes in controls (cf. dotted vs. dashed lines in Fig. 5; two-tailed revised standardized difference tests: $p>0.05$ [corrected]). Hence, while patient W.E.'s visual search behavior outside the scanner was pathologically shifted towards the right, MVS inside the scanner led to a decrease of this bias of search behavior; the magnitude of his leftward shift (towards the center) was indistinguishable from the leftward shift of controls.

Discussion

The present findings demonstrate that the bias of spatial attention and exploration in a patient with spatial neglect is indeed reduced by MVS. Lying in a 3T scanner ameliorated the patient's ipsilesionally biased distribution of overt attention and the corresponding neglect on the left of the search-space.

The present results closely resemble the known effects of caloric vestibular stimulation (CVS) on spatial exploration and orientation in neglect patients. When their left external auditory canal was irrigated with cold water, stroke patients with spatial neglect showed a reduction of their neglect of contralesionally located stimuli (Rubens, 1985; for review cf. Rossetti & Rode, 2002) as well as of their biased distribution of overt attention in visual search (Karnath et al., 1996). Moreover, it has been demonstrated that the typical bias in subjective straight-ahead body orientation in neglect patients is reduced by CVS (Karnath, 1994). Conversely, in healthy subjects CVS in darkness induces a bias in subjective straight-ahead (SSA), mimicking the bias of the SSA in neglect patients towards their ipsilesional side (e.g. Karnath, 1994; Chokron & Imbert, 1995; Kapoor et al., 2001). Finally, CVS biases healthy subjects' scan path during visual search (Karnath et al., 1996). When exploring their surroundings for possible targets, subjects' eye movements are no longer symmetrically distributed in the horizontal dimension but biased towards the side of cold CVS. To summarize, the present results in a patient with spatial neglect as well as the previous observations in healthy subjects by Lindner et al. (2021) demonstrate a close physiological correspondence of MVS and CVS. The two types of vestibular stimulation evoke very similar if not identical behavioral effects in healthy subjects as well as in stroke patients with spatial neglect.

However, regarding the use of vestibular stimulation in the rehabilitation of spatial neglect, MVS is superior to CVS. While CVS is highly unpleasant due to the application of cold water to the ear, the physiological effect of MVS does not evoke any unpleasant sensations; actually, it is not even directly perceived while the subject lies in the scanner. More importantly, the effect of CVS (in healthy subjects as well as in patients with neglect) lasts only a few minutes, while the physiological effect of MVS persists for the entire time while the subject lies in the scanner (Roberts et al., 2011; Jareonsettasin et al., 2016). So far, this has been shown for a time period of 90 minutes inside a 7T scanner. During this time, the horizontal nystagmus diminished but persisted and did not extinguish (Jareonsettasin et al., 2016). Thus, for therapeutic considerations in spatial neglect, MVS is the much more appropriate type of vestibular stimulation. The tonic nature of MVS could serve as a noninvasive and comfortable means to continuously stimulate the labyrinth of stroke patients with spatial neglect. However, whether MVS is actually suitable for reducing neglect symptoms in a therapeutic sense, i.e., whether it might help to induce longer-term plastic changes in the patients' pathologically altered spatial representations, still remains to be proven in future studies. In addition, the cost, availability, and exclusion criteria of MRI as well as the patient's potential burden associated with lying in the narrow tube of an MRI scanner must also be weighed against any potential therapeutic benefit. Nevertheless, the present study supports the idea that an intervention as simple as lying in a 3T MRI scanner helps reduce spatial neglect through MVS.

Acknowledgements

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