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RESEARCH ARTICLE

Acute peripheral vestibular deficit increases redundancy in random number generation

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Abstract Unilateral peripheral vestibular deficit leads to broad cognitive difficulties and biases in spatial orientation. More specifically, vestibular patients typically show a spatial bias toward their affected ear in the subjective visual vertical, head and trunk orientation, fall tendency, and walking trajectory. By means of a random number generation task, we set out to investigate how an acute peripheral vestibular deficit affects the mental representation of numbers in space. Furthermore, the random number generation task allowed us to test if patients with peripheral vestibular deficit show evidence of impaired executive functions while keeping the head straight and while performing active head turns. Previous research using galvanic vestibular stimulation in healthy people has shown no effects on number space, but revealed increased redundancy of the generated numbers. Other studies reported a spatial bias in number representation during active and passive head turns. In this experiment, we tested 43 patients with acute vestibular neuritis (18 patients with left-sided and 25 with right-sided vestibular deficit) and 28 age-matched healthy controls. We found no bias in number space in patients with peripheral vestibular deficit but showed increased redundancy in patients during active head turns. Patients showed worse performance in generating sequences of random numbers, which indicates a deficit in the updating component of executive functions. We argue that RNG is a promising candidate for a time- and cost-effective assessment of executive functions in patients suffering from a peripheral vestibular deficit.

Keywords Vestibular deficit · Numerical cognition · Random number generation · Spatial attention · Executive functions

Introduction

There is a growing interest in the cognitive consequences of peripheral vestibular deficits (PVD). Cognitive difficulties of patients with PVD have been clinically and empirically identified in the domains of attention, executive functions, numerical cognition, spatial memory, reading, and various dual tasks combining cognitive tasks with balance demands (for reviews see Bigelow and Agrawal 2015; Hanes and McCollum 2006; Mast et al. 2014; Smith et al. 2005). The consequences of PVD on spatial cognition have received special attention. Human and animal studies report impaired spatial memory and hippocampal atrophy following bilateral vestibular loss (Brandt et al. 2005; Russell et al. 2003; Schautzer et al. 2003; Stackman and Herbert 2002). Interestingly, neither impaired spatial memory nor hippocampal atrophy has been found in patients with unilateral PVD (Hufner et al. 2007). Nevertheless, these patients show distinct patterns of spatial biases across a wide range of tasks; typically directed toward their affected side: Fall tendency (Brandt 2003), walking trajectory deviation (Borel et al. 2004), and deviation of the subjective visual vertical (Friedmann 1970; Halmagyi et al. 1991; Vibert and Hausler 2000) are among the most frequently found symptoms in patients with unilateral PVD. Taken

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together, these symptoms suggest that asymmetric vestibular stimulation in unilateral PVD leads to global and fast-adaptive changes in internal spatial representations (Borel et al. 2008; Péruch et al. 2005; vonBrevern et al. 1997). This view has received further support from research in healthy participants. It has been shown that passive body rotations around the earth-vertical axis can laterally shift visual, auditory, and tactile attention (Figliozzi et al. 2005; Schueli et al. 1999).

In the present study, we set out to investigate the effects of acute PVD on the spatial representation of numbers. According to the mental number line hypothesis, numbers are internally mapped onto a left-to-right oriented number line (Dehaene et al. 1993). The random number generation (RNG) task is a widely used tool to investigate the spatial properties of number space (Badets et al. 2012; Cheng et al. 2015; Di Bono and Zorzi 2013; Ferrè et al. 2013; Grade et al. 2013; Hartmann et al. 2012; Loetscher and Brugger 2007, 2009; Loetscher et al. 2008; Shaki and Fischer 2014). Intriguingly, spatial biases in RNG tasks seem to be correlated with visual number line bisection and in some cases, with orientation biases in real space (Loetscher and Brugger 2007).

Equally important, RNG tasks are also frequently used as a measure of executive functions in terms of updating and inhibition (Audiffren et al. 2009; Daniels et al. 2003; Ferrè et al. 2013; Friedman and Miyake 2004; Loetscher and Brugger 2009; Miyake et al. 2000; Peters et al. 2007; Sexton and Cooper 2014; Towse and Neil 1998). In RNG tasks, participants are typically instructed to produce a series of random numbers from a certain response set at a constant time rate. The instruction implicitly entails that all numbers from the response set should be produced equally often (“equipotentiality criterion”). The adherence to this task-inherent rule requires keeping track of recent responses (updating). Furthermore, it requires the inhibition of stereotypical sequences like counting (see Friedman and Miyake 2004; Miyake et al. 2000; Towse and Neil 1998 for the underlying factor structure of the RNG task). The involvement of executive functions is also supported by neuroimaging studies that report the activation of the dorsolateral prefrontal cortex during RNG tasks (Daniels et al. 2003; Jahanshahi et al. 2000).

Recent studies have found interesting links between vestibular function and performance in RNG tasks in terms of both spatial orientation and executive functions. Active head–body motion to the right is associated with the production of more large numbers compared to head motion to the left (Cheng et al. 2015; Loetscher et al. 2008; Shaki and Fischer 2014). Similar findings have been reported for passive whole-body-motion using a motion platform (Hartmann et al. 2012). Taken together, these results suggest that vestibular information affects attention allocation processes on higher cognitive representations such as the mental number line. Further evidence for this effect has been reported in neglect patients. Vestibular stimulation by galvanic or caloric vestibular stimulation has been shown to alleviate neglect symptoms (Karnath and Dieterich 2006; Utz et al. 2010, 2011). Interestingly, neglect patients misplace the midpoint of a numerical interval toward the larger number, which matches their difficulties in bisecting physical lines (Priftis et al. 2012; Zorzi et al. 2002). Neglect patients and patients with unilateral PVD share common spatial biases with respect to eye and head orientation in the horizontal plane, and the subjective straight ahead (Choi et al. 2014; Hamann et al. 2009; Hornsten 1979; Karnath and Dieterich 2006; Richard et al. 2004). Considering the common spatial biases, it is conceivable that patients with unilateral PVD exhibit a similar bias in number space. Unlike other studies on number bisection in neglect patients, Loetscher and Brugger (2009) did not find a bias in the number space when applying a RNG task. Furthermore, Ferrè et al. (2013) found increased redundancy during galvanic vestibular stimulation (GVS), however, no differences in the magnitude of produced numbers as compared to sham stimulation. Taken together, it is yet unclear whether vestibular information affects number space.

Using the RNG task, we examined whether unilateral PVD results in increased redundancy, stereotyped response behavior, or biases in number space. Based on the paradigm from Loetscher et al. (2008), we examined RNG performance while keeping the head straight and while performing active head turns. Including the latter is crucial since previous research has produced ambiguous results with respect to interference between cognitive performance and simultaneous postural challenges in patients with PVD. Some studies revealed increased impairment under dynamic conditions (Nascimbeni et al. 2010; Roberts et al. 2011; Talkowski et al. 2005), while others report similar impairment under both static and dynamic conditions (Yardley et al. 2001; Redfern et al. 2004). In line with Ferrè et al.’s (2013) study using GVS in healthy participants and the frequently reported cognitive difficulties in vestibular patients, we hypothesized that unilateral PVD leads to a decreased ability to produce random numbers according to the “equipotentiality criterion”. We expected increased redundancy in patients with PVD in both conditions but a more pronounced effect in the dynamic condition (i.e., while performing head turns). In contrast, we did not expect unilateral PVD to result in stereotyped response behavior (counting), which is a typical sign of severe cognitive impairment (Brugger et al. 1996; Spatt and Goldenberg 1993). Finally, we did not have clear hypotheses whether to expect a bias in the number space of patients with acute unilateral PVD. The existing empirical data suggest three possible outcomes: (1) In line with neglect-like symptoms of spatial orientation (Karnath and Dieterich 2006), patients with unilateral PVD might exhibit a bias in number space directed toward their affected ear (i.e., producing larger numbers following right-sided PVD and vice versa). (2) In contrast, they might show a bias toward their healthy ear (i.e., producing smaller numbers following right-sided PVD). This is suggested from research in healthy participants, who show a bias toward the side with increased firing rate of the vestibular nerve, i.e., the side in direction of the turn (Figliozzi et al. 2005; Hartmann et al. 2012; Loetscher et al. 2008). (3) Lastly, the results by Ferrè et al. (2013) suggest no influence of asymmetric vestibular stimulation on number space, and therefore we may expect no difference between left- and right-sided vestibular patients. Furthermore, the frequency of contralesional neglect symptoms is equal to that of ipsilesional neglect symptoms in patients with PVD (Choi et al. 2014). Another study reported that patients with unilateral PVD show a shift of visual attention, which was, however, uncorrelated with lesion side (Popp et al. 2015). The existence of spatial hemineglect in acute PVD remains controversial as none of the patients in a recent study have fulfilled the diagnostic criteria of spatial hemineglect (Conrad et al. 2015).

Despite or rather because of the conflicting and scarce literature, it is crucial to further our understanding of the cognitive consequences of PVD in order to treat vestibular patients adequately. In our view, the RNG task might be a suitable candidate to achieve this goal since it tackles two concepts—namely executive function and attention allocation—where difficulties are often reported in vestibular patients.

Methods

Participants

Between January 2014 and December 2015, we tested fifty patients with acute PVD attributed to viral infection (vestibular neuritis). All patients were diagnosed with vestibular neuritis after extensive neurootological examination including electronystagmography with bithermal caloric testing, pendular rotatory chair testing, cervical vestibular evoked myogenic potentials (cVEMPs), video head impulse test (V-HIT), subjective visual vertical (SVV), and dynamic visual acuity test (DVA). To assess the subjective handicapping effects of their vestibular disease, all participants filled out the dizziness handicap inventory (DHI; Jacobson and Newman 1990). They were tested during a routine follow-up after they presented with acute symptoms of vertigo at the emergency ENT-unit of the University Hospital Bern (mean interval = 15.6 days after initial admission). We only included patients with (1) a canal paresis of 20% or more as revealed by caloric testing, (2) no hearing loss, (3) no neurologic signs indicative of vertigo due to a central lesion, (4) no history of previous neurootologic diseases. The final sample consisted of 18 patients with left-sided and 25 patients with right-sided PVD. Seven patients were excluded because they did not meet the inclusion criteria described above. Additionally, we tested 28 age-matched healthy participants. Inclusion criterion was the absence of previous neurologic or neurootological diseases. Demographic and clinical data of the final sample are provided in Table 1.

All participants gave informed consent prior to the experiment. The study was approved by the local ethics committee. Testing was conducted according to the ethical standards laid out by the Declaration of Helsinki.

Table 1 Demographic and clinical data of the patients with left-sided and right-sided vestibular neuritis and healthy controls

Side of lesion	Patients		Controls
	Left	Right	None
Sample size	18	25	28
Age (*M*; SD)	44.0 (17.2)	56.6 (14.7)	46.5 (16.8)
Handedness (right/left)	17/1	24/1	26/2
Caloric testing (hyporeflexia/areflexia)	16/2	19/6	–
Pendular rotatory chair			
Preponderance left	0	12	–
Preponderance right	5	1	–
Symmetric	9	11	–
n.a.	4	1	–
V-HIT (reduced gain[a]/normal gain/n.a.)			–
Left horizontal SCC	11/7/0	0/25/0	–
Left anterior SCC	11/5/2	4/21/0	–
Left posterior SCC	4/14/0	4/21/0	–
Right horizontal SCC	0/18/0	14/11/0	–
Right anterior SCC	1/15/2	13/12/0	–
Right posterior SCC	3/15/0	8/17/0	–
SVV (mean deviation from vertical in °)	−1.97	+2.04	–
cVemps (absent/present/n.a.)			
Left saccular function	4/14/0	6/19/0	–
Right saccular function	2/16/0	12/13/0	–
DVA (pathological[b]/normal/n.a.)			
Left horizontal SCC	2/11/5	2/19/4	–
Right horizontal SCC	3/10/5	4/17/4	–

na *not assessed, SCC* semicircular canal

[a] Gain values <0.7 were considered reduced

[b] See Li et al. (2014) for normative DVA values

Random number generation task

Following the paradigm of Loetscher et al. (2008), participants were instructed to produce a sequence of random numbers. They were asked to keep their eyes closed during the task and generate numbers at a steady pace of 0.5 Hz, which was indicated by a metronome. The response set was restricted to numbers between 1 and 30. The task was performed twice. First with the instruction to generate numbers while keeping the head straight (static condition), a second time while performing rhythmic head turns in the horizontal plane (dynamic condition). In the latter, participants were instructed to turn their head in time with the pace of the metronome, and to produce a number at each turning point. They were asked to comfortably turn their head "as far as possible" to the left and to the right. The task was stopped after 40 generated numbers in the static condition and 80 numbers in the dynamic condition, i.e., after 40 responses at each turning point.

Data analysis

For all dependent measures, we computed planned contrasts to test two hypotheses: First, unilateral PVD might have a general effect on RNG performance (generic hypothesis). We thus contrasted the average of the patients with left- and right-sided PVD with the healthy controls. Second, we examined the influence of lesion side (specific hypothesis) and compared the two patients groups (left vs. right-sided PVD). See Ferrè et al. (2013) for analogous analyses comparing sham stimulation with left- and right-anodal galvanic vestibular stimulation.

In order to investigate the spatial bias in the RNG task, we compared the means of generated numbers and the proportion of small numbers (1–15) with a repeated-measures analysis of variance (ANOVA). We analyzed the between-subject variable group (left-sided PVD vs. right-sided PVD vs. healthy controls) in terms of the planned contrasts for the generic and specific hypothesis. The within-subject variable direction of head turn (left turn vs. right turn vs. static) was analyzed by means of an omnibus F-test (in analogy to Loetscher et al. 2008). Furthermore, we compared the sums of first-order differences (FODs, i.e., the differences between successive numbers) as an additional measure of number bias. Given the number range from 1 to 30, FODs could vary between −29 and +29. Positive FODs represent occurrences of ascending pairs of successive numbers (e.g., +5 for a response "11" followed by "16"), negative FODs represent occurrences of descending pairs (e.g., −3 for "18" followed by "21").

The randomness of a given sequence of numbers was calculated with the redundancy score (*R* score). This measure reflects the degree of deviation from the equiprobability of all response alternatives. The *R* score was calculated according to Towse and Neil (1998):

$$R \text{ score} = 100 \times \left(1 - \frac{\log_2 n - \frac{1}{n}\sum_i^a (n_i \times \log_2 n_i)}{\log_2 a}\right)$$

where n is the number of responses (i.e., the length of the randomly produced sequence), n_i is the number of occurrences of each response alternative i, and a is the number of response alternatives (set size). *R* score values range from 0 to 100 and express the deviation of a given sequence from perfect equipotentiality ($\log_2 a$), with higher values indicating a stronger sampling bias (i.e., more redundancy, less randomness). It is important to mention that the number of responses (40 numbers in the static, 80 numbers in the dynamic condition) was not a multiple of the set size. Consequently, it was not possible for participants to achieve perfect equipotentiality of all response alternatives. The lowest possible *R* score in the present study was 1.731 for the static condition and 0.483 for the dynamic condition. Additionally, we calculated the Adjacency combined score (Ac score), which is defined as the percentage of ascending and descending pairs of adjacent numbers (e.g., "6" followed by "7" or "4" followed by "3," respectively). The Ac score is thus indicative of stereotyped response behavior (i.e., forward and backward counting). *R* score, FODs, and Ac score were computed using RGcalc, an open-source software to quantify random number generation behavior (see Towse and Neil 1998 for a comprehensive description of the parameters and the software).

FODs, R, and Ac scores need to be based on all numbers generated within a given sequence. Unlike the analysis for the mean numbers, we thus calculated these parameters for the static and dynamic condition and did not split the numbers in the dynamic condition according to the direction of head turn after which they were produced (left turn vs. right turn). Furthermore, we decided to perform separate analyses for the static and the dynamic condition since the two conditions differed in the number of responses (40 in the static and 80 in the dynamic condition). Changes in task characteristics (e.g., number of responses) strongly influence RNG parameters (see Brugger 1997 for a review), and therefore the interpretation of a within-subjects factor condition (static vs. dynamic) is problematic. For example, it was easier to reach a low level of redundancy in the dynamic condition (80 responses) because any repetition of a single number had a smaller impact on the redundancy score compared to the static condition (40 responses). At the same time, the dynamic condition involved a double-task situation (head-turning and RNG), which had a potentially negative impact on RNG performance. Furthermore, the dynamic condition involved additional demands and could not be completed by 6 out of 43

PVD patients due to vertigo or the inability to follow the pace of the metronome.

Due to unequal sample sizes of the patients with PVD and healthy controls, we assessed homogeneity of variance (Levene's test) in case of the planned contrasts for the FODs, R, and Ac scores. Sphericity (Mauchly's test) was assessed in case of the repeated-measures ANOVA for the mean of generated numbers and the proportion of small numbers. There was no violation of homogeneity of variance (all $p > .115$) or sphericity (all $p > .260$) in none of the analyses expect for the Ac score in the static condition ($p = .045$) where we applied Welch's t test for unequal variances.

Results

Number space

We did not find evidence for a bias in number space as a consequence of unilateral PVD. The repeated-measures analysis of variance (ANOVA) showed no effect of group [$F(2, 62) = 0.919$, $p = .404$, $\eta_p^2 = .029$] on the mean of the generated numbers. More specifically, the planned contrasts for the generic (patients with unilateral PVD vs. healthy controls) and the specific hypothesis (left-sided vs. right-sided PVD) were not significant, with $t(62) = 0.001$, $p = .980$, $\eta_K = .004$ and $t(62) = 1.348$, $p = .183$, $\eta_K = .170$, respectively. The means of the generated numbers showed no difference between healthy controls ($M = 14.80$, SD = 1.23) and patients with left-sided ($M = 14.57$, SD = 1.50) and right-sided unilateral PVD ($M = 15.05$, SD = 1.23). Furthermore, there was no effect of the direction of head turn [$F(2, 124) = 0.307$, $p = .736$, $\eta_p^2 = .005$]. Participants' mean of generated numbers did not differ between the static condition ($M = 14.73$, SD = 1.24), and the dynamic left ($M = 14.81$, SD = 1.35) and right head turns ($M = 14.93$, SD = 1.34). There was no interaction group x direction of head turn [$F(4, 124) = 1.304$, $p = .272$, $\eta_p^2 = .040$]. Similarly, the planned contrasts for the generic [$t(62) = 0.058$, $p = .954$, $\eta_K = .007$] and the specific hypothesis [$t(62) = 1.105$, $p = .274$, $\eta_K = .139$] were not significant when comparing the groups in terms of the proportion of small numbers. There was no effect of the direction of the head turn [$F(2, 124) = 0.401$, $p = .670$, $\eta_p^2 = .006$], and group x direction of head turn did not interact [$F(4, 124) = 1.493$, $p = .208$, $\eta_p^2 = .046$].

Testing the generic hypothesis, the sum of positive FODs showed no difference between patients with unilateral PVD and healthy controls, neither in the static [$t(68) = -0.238$, $p = .813$, $\eta_K = .029$] nor the dynamic condition, respectively [$t(62) = -1.026$, $p = .309$, $\eta_K = .126$]. The effect was also absent for the sum of negative FODs, both for the static [$t(68) = 0.419$, $p = .677$, $\eta_K = .050$] and the dynamic condition [$t(62) = 1.050$, $p = .298$, $\eta_K = .129$]. Similarly, with respect to the specific hypothesis, the sum of positive FODs did not differ between patients with left-sided PVD and right-sided PVD in the static condition [$t(68) = -0.124$, $p = .902$, $\eta_K = .015$] and the dynamic condition [$t(62) = -1.617$, $p = .111$, $\eta_K = .199$]. The sum of negative FODs showed no differences in the static [$t(68) = -0.089$, $p = .929$, $\eta_K = .010$] and the dynamic condition [$t(62) = 1.806$, $p = .076$, $\eta_K = .221$] (Table 2).

Randomness

Interestingly, there was a significant difference in R scores between patients with unilateral PVD and healthy controls (generic hypothesis) in the dynamic condition [$t(62) = 2.450$, $p = .017$, $\eta_K = .296$]. Patients with unilateral PVD ($M = 8.08$, SD = 2.74) showed more redundancy in their sequences compared to healthy controls ($M = 6.41$, SD = 2.55). In contrast, there was no difference in the static condition [$t(68) = 1.257$, $p = .213$, $\eta_K = .148$]. Furthermore, we did not observe differences in redundancy between left- and right-sided PVD (specific hypothesis) for the static [$t(68) = 1.570$, $p = .121$, $\eta_K = .296$] and dynamic condition [$t(62) = 0.306$, $p = .761$, $\eta_K = .037$] (Fig. 1).

Stereotyped response behavior

With respect to the Ac score, there was no evidence in favor of the generic or the specific hypothesis. Patients with unilateral PVD and healthy controls did not differ, neither in the static condition [$t(47.281) = -1.248$, $p = .218$, $\eta_K = .181$] nor in the dynamic condition [$t(62) = -0.216$, $p = .830$, $\eta_K = .027$]. Furthermore, there were no differences between patients with left- and right-sided PVD in the static [$t(40.397) = -0.303$, $p = .763$, $\eta_K = .047$] and dynamic condition [$t(62) = -0.104$, $p = .918$, $\eta_K = .013$].

Further analyses

In order to control for a potential influence of age-related cognitive decline on RNG performance, we matched the healthy controls for age. In fact, planned contrasts showed that the final sample of patients with unilateral PVD did not differ from the healthy controls [$t(68) = 0.937$, $p = .352$, $\eta_K = .108$].

Furthermore, we tested whether the patients' increased R scores were related to recent hospitalization or self-perceived handicap in everyday situations. However, neither the time interval since emergency hospitalization ($r = -.088$, $p = .613$) nor the self-perceived handicap measured with the DHI ($r = -.009$, $p = .958$) correlated significantly with the R scores.

Table 2 Measures of spatial bias in number space for patients with left- or right-sided vestibular neuritis, and healthy controls under the static and the dynamic head-turning conditions

Condition	Side of vestibular neuritis						Healthy controls		
	Left			Right					
	Static	Dynamic		Static	Dynamic		Static	Dynamic	
		Left	Right		Left	Right		Left	Right
Mean number (SD)	14.76 (1.19)	14.44 (1.67)	14.51 (1.69)	15.03 (1.19)	15.06 (1.11)	15.05 (1.42)	14.49 (1.30)	14.82 (1.30)	15.09 (1.69)
Proportion of small numbers	54.22 (8.20)	57.34 (9.20)	55.78 (8.45)	53.33 (7.51)	53.33 (5.55)	53.69 (8.01)	56.16 (8.48)	54.46 (8.78)	52.95 (6.20)
Negative first-order differences (SD)	17.50 (3.70)	34.00 (6.28)		17.60 (3.98)	37.62 (5.95)		17.18 (3.26)	34.21 (5.97)	
Positive first-order differences (SD)	22.50 (3.70)	45.56 (6.50)		22.36 (3.96)	42.29 (5.93)		22.64 (3.36)	45.50 (6.02)	

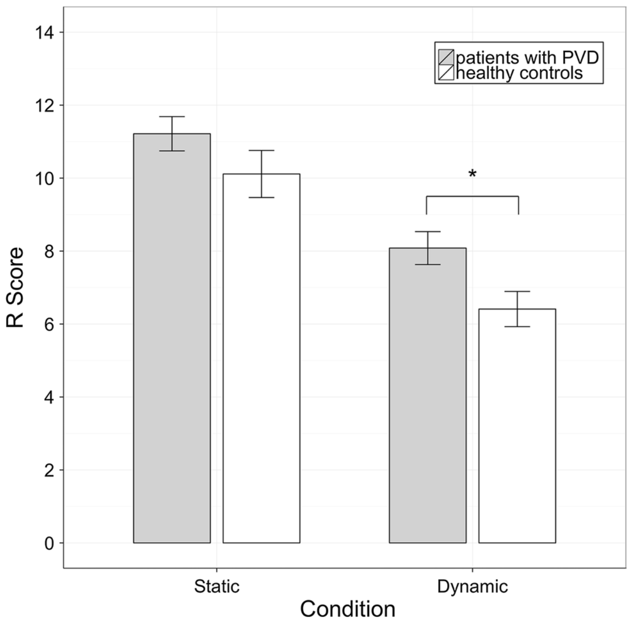

Fig. 1 Mean *R* scores in the static and dynamic condition. In average, patients with unilateral PVD showed reduced randomness (i.e., increased *R* scores) in the dynamic condition compared to the healthy controls. *Error bars* represent ± 1 SEM. *Asterisk* indicates significant differences ($p < .05$)

The static and dynamic conditions in the paradigm of Loetscher et al. (2008) differ with respect to the amount of random numbers that need to be produced (40 numbers in the static condition vs. 80 numbers in the dynamic condition, respectively). In order to assess whether the group difference in the dynamic condition could also be revealed with 40 numbers, we performed an additional analysis on the first 40 generated numbers of the dynamic condition. However, there was no significant difference in *R* scores between patients with unilateral PVD and healthy controls [$t(68) = 1.284$, $p = .204$, $\eta_K = .159$].

Discussion

In our experiment, we compared the RNG performance of patients with unilateral PVD and healthy controls. We examined whether acute unilateral PVD results in a bias of number space as measured by the magnitude of the randomly generated numbers and the occurrences of positive and negative FODs between successive pairs of generated numbers. Furthermore, since the RNG task is a widely used tool in neuropsychological testing, we also assessed whether the patients with PVD and healthy controls differ with respect to the randomness of the generated numbers and the use of stereotyped response behavior.

Randomness/response stereotypy

Compared to healthy controls, patients with PVD showed increased redundancy in their sequences of randomly generated numbers while performing rhythmic head turns. In other words, under dynamic conditions, they demonstrated poorer performance in producing random numbers according to the task-inherent equipotentiality criterion. As expected, we did not observe signs of stereotyped response behavior (i.e., counting), which are typically only found in patients with severe neurological diseases (Brugger et al. 1996; Spatt and Goldenberg 1993). Furthermore, we did not find group differences in the magnitude of generated numbers or first-order differences indicative of a bias in number space. Taken together, the findings strongly resemble those previously reported by Ferrè et al. (2013). In their experiment, there was no evidence for a bias in number space induced by asymmetric vestibular stimulation using GVS. However, they found increased redundancy during right-anodal, left-cathodal galvanic vestibular stimulation (R-GVS), which mimics an inhibition of the right vestibular input (Fitzpatrick and Day 2004; Goldberg et al. 1984). Unlike their specific effect of an artificial temporary right-sided vestibular lesion, our results support the notion of generally detrimental effects of unilateral PVD on cognitive functions, irrespective of lesion side.

In line with this notion, cognitive difficulties in patients with unilateral PVD have been reported in a growing body of the literature (Bigelow and Agrawal 2015; Hanes and McCollum 2006; Mast et al. 2014; Smith et al. 2005). The ability to produce random numbers according to the task-inherent equipotentiality criterion relies on the updating component of executive functions (Friedman and Miyake 2004; Miyake et al. 2000; Towse and Neil 1998). It requires the participant to keep track of recently produced numbers in order to avoid a sampling bias. Our results are consistent with the existing, however, scarce literature addressing executive functions in patients with PVD. Grimm et al. (1989) found executive function deficits across different tasks in patients with perilymph fistula syndrome. Their results might, however, have been confounded by the concomitant head injury of the patients. Other studies in patients with central and peripheral vestibular deficit reported difficulties in counting backwards, in the arithmetic subtest of the Wechsler Adult Intelligence Scale (Risey and Briner 1990), and in prioritizing tasks (Black et al. 2004). In contrast, a recent study by Bigelow et al. (2015) did not find consistent associations between vestibular function and performance in executive function tests. However, it has to be pointed out that their study was different with respect to the experimental set up. First, their participants were recruited from a prospective cohort study of the general population (Baltimore Longitudinal Study of Aging) and the study did not specifically target patients with diagnosed PVD. Second, vestibular functioning was only assessed by means of cVemps measuring saccular function, while we administered a broad range of neurootological tests assessing both canal and otolith functions.

It is important to note that we only found decreased redundancy of patients with PVD in the dynamic condition. Due to the unequal amount of random numbers that need to be produced in the paradigm developed by Loetscher et al. 2008 (40 numbers in the static vs. 80 numbers in the dynamic condition, respectively), it is difficult to disentangle whether the difference in the dynamic condition was driven by the dual-task induced by the head movements or by the greater number of trials. The former implies that the updating deficit of patients with PVD in the dynamic condition might merely reflect a global cognitive impairment in dual tasks combining a cognitive task with simultaneous head movements. In fact, cognitive deficits are more pronounced when adding a simultaneous postural challenge. However, it has to be noted that substantial evidence suggests that cognitive impairment in PVD also exists when the same tasks are tested under static conditions (Yardley et al. 2001; Redfern et al. 2004; Talkowski et al. 2005). More importantly, previous tasks showing executive deficits in vestibular patients were all performed under static conditions (Bigelow et al. 2015; Black et al. 2004; Grimm et al. 1989; Risey and Briner 1990). Thus, it is conceivable that the 40 numbers are not sensible enough to detect a static updating deficit. Indeed, an additional analysis with the first 40 numbers of the dynamic condition revealed no difference between patients with PVD and healthy controls. In line with previous research indicating executive deficits under static conditions (Bigelow et al. 2015; Black et al. 2004; Grimm et al. 1989), an updating deficit might also be revealed in the static condition when using a longer sequence of random numbers (i.e., 80 numbers). Thus, future research should adapt the RNG paradigm in order to allow for a better comparison between the static and dynamic condition. Irrespective of static deficits, the dynamic RNG task offers a promising opportunity to identify patients with PVD who are at risk in everyday situations that combine the need for updating with simultaneous postural challenges. For instance, regular head-turning while updating the current traffic situation is crucial for driving a vehicle or walking in crowded places. From a clinical perspective, testing cognitive performance under dynamic conditions is more important than assessing task performance under static conditions.

As a limitation of our study, we did not assess the educational level of the patients with PVD. However, it is unlikely to play a role and considering the extensive literature on variables influencing RNG performance, there is strong evidence that education and even statistical or mathematical proficiency does not affect the performance in different randomization tasks including RNG (Brugger 1997; Pettigrew et al. 1982; Treisman and Faulkner 1987; Ward 1973). Moreover, it is possible that reduced RNG performance might be a general consequence of a handicapping disease or recent hospitalization, unspecific to the involvement of the vestibular system. Using healthy people as controls, we are not able to completely rule out this possibility. However, we have good reasons to believe that it does not explain the observed difference between the patients with PVD and the healthy controls. First, the mean interval between emergency hospitalization and testing was relatively large. Second, the interval since hospitalization was unrelated to randomness performance. Third, the subjective handicapping effects of the vestibular disease were not related to randomness performance either.

To date, cognitive difficulties in PVD have been frequently reported across many domains. However, the findings often remain descriptive, without providing explanations for the underlying mechanisms of cognitive difficulties encountered in PVD. Future studies would benefit from structural and functional examinations at the neuronal level, combining cognitive testing with neuroimaging. Valuable insights have already been gained with respect to the spatial memory deficits, revealing concomitant hippocampal atrophy in patients with bilateral PVD (Brandt et al. 2005). Furthermore, patients with bilateral PVD also show reduced resting-state connectivity in parieto-insular areas that receive vestibular afferents (Gottlich et al. 2014). Acute unilateral PVD leads to a complex pattern of metabolic changes within the cortical vestibular system. Glucose metabolism is upregulated in parieto-insular areas and simultaneously downregulated in visual, auditory, and somatosensory areas including the inferior and superior parietal cortex (Bense et al. 2004; Dieterich and Brandt 2008). Interestingly, RNG involves widespread cortical activations in the dorsolateral prefrontal cortex, the anterior cingulate, the inferior and superior parietal cortex, the premotor cortex, and the cerebellum (Daniels et al. 2003; Jahanshahi et al. 2000). We hypothesize that metabolic downregulations in parietal areas during the acute stage of PVD are responsible for the observed decrease in randomness in the RNG task.

Number space

Taking into account the rather conflicting results from previous studies, we did not have clear hypotheses regarding a possible bias in the number space of patients with PVD. Our results suggest that patients with PVD do not differ from healthy controls, neither under static nor dynamic conditions. Furthermore, patients with left- and right-sided PVD did not differ from each other with respect to the magnitude of the randomly produced numbers and FODs. Consequently, we found no evidence for a bias in number space following acute unilateral PVD. Unlike patients with unilateral PVD, studies in healthy participants showed changes in RNG tasks during head motion (Hartmann et al. 2012; Loetscher et al. 2008; Shaki and Fischer 2014). The findings from this study are inconsistent with the notion that vestibular impairment leads to changes in internal spatial representations (Borel et al. 2008). However, our result is in line with Ferrè et al. (2013), who examined RNG behavior during GVS and did not observe a shift in number space. It is intriguing that studies in unilateral PVD and GVS fail to reproduce the number biases found with real motion. We argue that two mechanisms are responsible for the inconsistencies in previous studies.

First, studies with real motion mostly applied motion profiles that made the horizontal plane salient (Cheng et al. 2015; Loetscher et al. 2008; Shaki and Fischer 2014; but see Hartmann et al. 2012 for an example of vertical plane saliency). In contrast, unilateral PVD and GVS lead to an unspecific tone imbalance in the vestibular nerve, resulting in diffuse sensations of subjective self-motion (Baloh et al. 2010; Brandt 2003; Curthoys and Macdougall 2012; Fitzpatrick and Day 2004; Goldberg et al. 1984; St George and Fitzpatrick 2011). This is an important difference because making the horizontal plane more salient through instructions in RNG tasks substantially increases number bias (Cheng et al. 2015; Loetscher et al. 2008). The role of saliency of the horizontal plane is consistent with the notion that several findings supporting the mental number line hypothesis are driven by short-term number space associations in working memory rather than long-term semantic representations (van Dijck and Fias 2011).

Second, asymmetric peripheral vestibular stimulation in PVD and GVS can exert opposite effects on spatial bias. On the one hand, PVD and GVS induce sensations of self-motion toward the side with elevated firing of vestibular neurons. On the other hand, PVD and GVS lead to compensatory reactions showing deviations of the subjective visual vertical, walking trajectory deviation, and fall tendency toward the ear with decreased firing rate (Borel et al. 2004; Brandt 2003; Friedmann 1970; Halmagyi et al. 1991; St George and Fitzpatrick 2011; Vibert and Hausler 2000). It is likely that the two processes can cancel each other out and thus prevent a consistent shift of attention on higher cognitive representations in unilateral PVD and GVS. This is a conceivable explanation for the absence of a number bias in the present study and Ferrè et al. (2013).

However, we cannot rule out the possibility that the absence of number bias was a consequence of low sensitivity of the RNG task to detect number bias. Previous studies in neglect patients have reported number bias by means of a numerical bisection task, numerical comparison to a standard, and mental arithmetic (Dormal et al. 2014; Vuilleumier et al. 2004; Zorzi et al. 2002). Interestingly, neglect patients did not show signs of number bias in a RNG task (Loetscher and Brugger 2009). It is thus possible that administering additional numerical tests could reveal an existing number bias in patients with unilateral PVD since it has been proposed that PVD might result in neglect-like symptoms (Karnath and Dieterich 2006). However, it has to be pointed out that recent research suggests that spatial biases only appear in a subset of patients with unilateral PVD and seem to be unrelated with lesion side (Choi et al. 2014; Popp et al. 2015). Furthermore, the notion of neglect in patients with unilateral PVD has recently been challenged by Conrad et al. (2015), who showed that patients with acute unilateral PVD do not fulfill the diagnostic criteria for neglect. In light of these findings, we think it is likely that the lack of group differences in this study represents a genuine absence of spatial biases in PVD.

Conclusions

Administering the RNG task, we found that patients with acute unilateral PVD are less able to produce random numbers under dynamic conditions. This indicates that acute unilateral PVD can adversely affect the updating component of executive functions, therefore adding evidence to the growing body of the literature reporting cognitive difficulties in vestibular patients. Not surprisingly, we did not find evidence for a deficit in inhibiting stereotyped responses (counting), which is a typical sign of severe brain damage. Furthermore, we did not observe a bias in number space following unilateral PVD. Reduced randomness could be explained by a transient downregulation of parietal areas during the acute stage of the disease. It is desirable that future studies examine the underlying mechanisms that lead to cognitive impairments in patients with PVD, and how they possibly relate to yet other difficulties with numbers such as dyscalculia (Smith 2012). Neuroimaging could help to explore whether reduced randomness in patients with PVD is related to the functional downregulation in parietal areas. We argue that RNG is a promising candidate for a time- and cost-effective assessment of executive functions in patients with PVD.

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