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Spatial orientation in patients with chronic unilateral vestibular hypofunction is ipsilesionally distorted

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HIGHLIGHTS

- Visual vertical (VV) was measured in 13 patients with chronic unilateral vestibular hypofunction.
- VV shifts in the patients were significant only when rolled ipsilesionally.
- Thus VV testing in roll-tilted positions is recommended to identify more subtle vestibular deficits.

ABSTRACT

Objective: Acute unilateral peripheral–vestibular hypofunction (UVH) shifts the subjective visual vertical (SVV) ipsilesionally, triggering central compensation that usually eliminates shifts when upright. We hypothesized that compensation is worse when roll-tilted.
Methods: We quantified SVV errors and variability in different roll-tilted positions (0°, ±45°, ±90°) in patients with chronic UVH affecting the superior branch (SVN; $n = 4$) or the entire (CVN; $n = 9$) vestibular nerve.
Results: Errors in SVN and CVN were not different. When roll-tilted ipsilesionally 45° (9.6 ± 5.4° vs. −0.2 ± 6.4°, patients vs. controls, $p < 0.001$) and 90° (23.5 ± 5.7° vs. 16.8 ± 8.8°, $p = 0.003$), the patient's SVV was shifted significantly towards the lesioned ear. When upright, only a trend was noted (3.6 ± 2.2° vs. 0.0 ± 1.2°, $p = 0.099$); for contralesional roll-tilts shifts were not different from controls. Variability was larger for CVN than SVN ($p = 0.046$). With increasing disease-duration, adjustment errors decayed for ipsilesional roll-tilt and upright ($p \leqslant 0.025$).
Conclusions: The reason verticality perception was distorted for ipsilesional roll-tilts, may be the insufficient integration of contralesional otolith-input. Similar errors in SVN and CVN suggest a dominant utricular role in verticality perception, albeit the sacculus may improve precision of SVV estimates.
Significance: With deficiencies in central compensation being roll-angle dependent, extending SVV-testing to roll-tilted positions may improve identifying patients with chronic UVH.

1. Introduction

Innervation of the vestibular organs is provided by two branches of the vestibular nerve: the superior branch receives input from the horizontal and anterior semicircular canal (SCC) and the utriculus, the inferior branch contains axons from the posterior SCC and the sacculus (Gianoli et al., 2005; Curthoys, 2010). Sudden unilateral peripheral–vestibular hypofunction (UVH) typically presents as acute vestibular syndrome (AVS) (Tarnutzer et al., 2011a), i.e., prolonged vertigo/dizziness accompanied by nausea/vomiting nystagmus, gait ataxia and motion intolerance, and may result from isolated superior vestibular neuropathy (SVN), inferior vestibular neuropathy (IVN) or a combination of both (CVN). The most frequent cause of UVH is inflammation of the vestibular nerve (Strupp and Magnusson, 2015). After acute UVH, symptoms such as vertigo/dizziness, imbalance of stance and spontaneous nystagmus resolve within days to weeks (Okinaka et al., 1993; Halmagyi et al., 2010). This is usually achieved by central compensatory mechanisms including re-weighting of multisensory (vestibular, somatosensory, visual) input (Angelaki and Cullen, 2008; Sadeghi et al., 2010) and by minimizing the vestibular tone

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imbalance between the affected and the healthy side (Halmagyi et al., 2010), as the vestibular nerve remains hypofunctional in the majority of cases. Whereas compensation allows about 80% of patients to resume normal activities of daily life (Reid et al., 1996; Halmagyi et al., 2010), these mechanisms are insufficient to compensate for fast movements, causing brief spells of vertigo and oscillopsia during rapid head movements (Okinaka et al., 1993; Halmagyi et al., 2010).

Patients with UVH misperceive the direction of gravity, as assessed behaviorally for example by the subjective visual vertical (SVV) (Van Beuzekom and Van Gisbergen, 2000; Tarnutzer et al., 2009a, 2012a). The SVV thereby shifts towards the lesioned side when upright (Friedmann, 1971; Curthoys et al., 1991; Bergenius et al., 1996; Anastasopoulos et al., 1997; Lopez et al., 2008). Healthy humans show a distinct pattern of roll-angle dependent SVV errors: while roll over-compensation occurs at small (<60°) and very large (>120–135°) (Tarnutzer et al., 2009a) angles (E-effect) (Mueller, 1916), roll under-compensation is found for medium-sized (60–135°) angles (A-effect) (Aubert, 1861). Most likely the A- and E-effect are of central origin and a consequence of the processing of visual input as previous studies reported an accurate percept of vertical for the subjective postural horizontal (Mittelstaedt, 1983) and the subjective haptic vertical (Schuler et al., 2010) and horizontal (Wade and Curthoys, 1997). The trial-to-trial variability of SVV adjustments is roll-angle dependent, showing an m-shaped pattern with minimal variability when upright, maximal values around 120–135° roll and intermediate values in upside-down position (Tarnutzer et al., 2009a).

To which extent the estimates of the direction of gravity recover over time after acute UVH and whether this holds true both for upright and roll-tilted positions is unclear. Albeit decreasing in size, adjustment errors may remain abnormal years after UVH (Tabak et al., 1997). It seems reasonable to assume that also for roll-tilted positions errors decrease over time, though since upright is a more common posture when walking, the rate of improvement may be different at roll-tilted angles. Both more extensive exposure to upright position or the brain prioritizing accurate verticality perception when upright may explain such differences. Therefore, the offset of the estimated direction of gravity may rather be roll-angle dependent than constant. With otolith sensors being polarized, i.e., preferentially sensing ipsilateral roll (Dai et al., 1989), unilateral loss may result in more pronounced errors when roll-tilted towards the lesioned side. Alternatively, as a strategy to compensate for acute UVH, the brain could rely more on body-fixed orientation cues, resulting in an increased A-effect and a decreased E-effect on both sides (Tarnutzer et al., 2011b). The few studies that have addressed adjustment errors in chronic UVH while roll-tilted suggest a tendency towards roll under-compensation at small angles (Dai et al., 1989; Böhmer and Rickenmann, 1995; Bergenius et al., 1996; Betts et al., 2000), while no data is available for larger angles. The aim of this study was to characterize both the accuracy and precision of SVV adjustments in chronic UVH over a larger range of roll-tilted positions. Assessing the SVV in roll-tilted positions may be a more sensitive test to detect residual deficits after UVH and will shed more light on potential compensatory mechanisms and the role of the different macular organs. The relative contribution of utricular and saccular afferents to internal estimates of vertical remains debated. While preserved verticality perception in patients with isolated acute inferior vestibular neuropathy suggests no significant saccular contribution to the SVV, combining utricular and saccular input and taking a higher number of utricular compared to saccular afferents (1:0.6 (Rosenhall, 1972)) into account, resulted in accurately simulated SVV responses (Tarnutzer et al., 2009a). Likewise, for the otolith-ocular reflex a ratio of utricular-to-saccular input of 3:1 was proposed (De Graaf et al., 1996). Numerical simulations demonstrated a smaller but still significant contribution of saccular afferents to the detection of head roll (Jaeger and Haslwanter, 2004). Based on these observations we would predict larger SVV errors and trial-to-trial variability in case of CVN compared to SVN. The completeness of utricular/saccular damage may also influence verticality perception. Partial utricular function may be sufficient for verticality perception, while only in case of complete utricular/saccular loss would adjustment errors emerge.

2. Material and methods

2.1. Subjects

We compared 13 right-handed patients with chronic UVH (CVN = 9, SVN = 4) with 17 healthy controls (Table 1). All patients had a history of vestibular neuropathy (VN; symptom onset 11.3 ± 5.9 months ago, mean ± 1 standard deviation, range = 3–21 months) except two patients with vestibular schwannoma. Written informed consent was obtained after a full explanation of the experimental procedure in all participants. The protocol was approved by the Cantonal ethics commission Zurich (KEK-ZH-2013-0054) and was in accordance with ethical standards laid down in the 2013 Declaration of Helsinki for research involving human subjects.

2.2. Experimental setting

All potential study participants received vestibular testing before inclusion and the pattern of the peripheral–vestibular deficit was determined. The video-head-impulse test (vHIT; GN Otometrics, Taastrup, Denmark) was used to evaluate horizontal and vertical canals. SCC-hypofunction was defined as a reduction in angular vestibulo–ocular reflex (aVOR) gain and/or the occurrence of compensatory saccades. For gains, cut-off values of 0.8 (horizontal canals) and 0.7 (vertical canals) were proposed by the manufacturer, which have recently been confirmed over a broad range of ages (McGarvie et al., 2015).

Sacculus function was assessed by cervical vestibular-evoked myogenic potentials (cVEMPs) and utriculus function by ocular vestibular-evoked myogenic potentials (oVEMPs). In all participants air-conducted cVEMPs (brief clicks at 500 Hz, 2 ms duration, 2 series with 200 stimuli each) were obtained at two different intensities (90 and 95 dB normal hearing level) and responses from the sternocleidomastoid muscle were recorded. Additional air-conducted cVEMPs at 100 dB hearing level were applied if responses at 90 and 95 dB were insufficient (see Rosengren et al. (2010)) for further details on cVEMPs). If air-conducted cVEMPs at 100 dB were inconclusive (e.g. bilaterally absent responses), bone-conducted cVEMPs were obtained as well. Only the asymmetry ratio (AR) derived from the highest stimulus intensity was considered and if both air-conducted and bone-conducted cVEMPs were obtained, only results from bone-conducted cVEMPs were used. For recording of oVEMPs, brief vibrations (500 Hz, 4 ms duration, two times 200 stimuli, provided by a Minishaker, 4810 from Brüel and Kjaer, Denmark) were applied to the forehead and responses from the inferior oblique muscles were recorded (see Weber and Rosengren (2015)) for details). Differences in response amplitude (left vs. right) of >30% or absent responses were considered abnormal for both oVEMPs and cVEMPs.

Hypofunction of the horizontal and the anterior semicircular canal on the video-head-impulse test (reduction in gain and/or presence of compensatory saccades) and significant loss of utricular function (AR > 30% with stronger responses on the opposite side on oVEMP-testing) accompanied by normal saccular function (AR ⩽ 30% on cVEMPs) were required to meet the criteria for a

Table 1
patients' characteristics and testing results (vHIT, cVEMPs, oVEMPs, VSS).

	Age (years)	Sex	Disease duration (months)	Lesioned side	Type of vestibular loss	vHIT of the affected side (gain)[a]			oVEMPs asymmetry ratio (%)	cVEMPs asymmetry ratio			VSS		
						Horizontal SCC	Anterior SCC	Posterior SCC		Conduction: air 90 dB	Air 95 dB	air 100 dB	Bone	VSS-total	VSS-VER	VSS-AA
P 01	53	f	3	Left	CVN	***0.32***	1.02[*]	0.93[*]	100	NA	90%	***100%***	NA	26	15	11
P 02	45	m	3	Left	CVN	***0.34***	***0.57***	***0.55***	100	50%	***53%***	NA	NA	6	3	3
P 03	67	f	8	Left	CVN	***0.24***	***0.62***	***0.47***	100	NA	NA	100%	***38%***	60	39	21
P 04	51	m	21	Left	CVN	***0.56***	0.94[*]	0.97[*]	100	100%	NA	45%	***48%***	6	3	3
P 05	29	m	31	Left	CVN[†]	***0.45***	0.77[*]	0.97[*]	80	NA	NA	100%	***100%***	16	9	7
P 06	53	m	10	Right	CVN	***0.55***	0.74[*]	0.78[*]	100	NA	NA	NA	***100%***	21	15	6
P 07	59	m	16	Right	CVN	0.84[*]	1.08[*]	0.84[*]	45	NA	NA	40%	***32%***	5	3	2
P 08	70	m	19	Right	CVN[‡]	***0.70***	***0.69***	0.99[*]	100	46%	NA	***51%***	NA	60	35	25
P 09	59	f	60	Right	CVN[†]	***0.76***	***0.29***	***0.54***	100	NA	NA	100%	***37%***	16	9	7
P 10	67	f	9	Left	SVN	***0.04***	0.75[*]	***0.22***	100	2%	19%	NA	NA	34	18	16
P 11	55	m	14	Left	SVN	***0.60***	0.80[*]	0.98	100	10%	12%	2%	NA	6	3	3
P 12	67	m	9	Right	SVN	***0.42***	***0.62***	***0.71***	100	32%	NA	23%	NA	15	7	8
P 13	35	m	12	Right	SVN	***0.62***	0.84[*]	0.93	100	11%	NA	2%	NA	6	3	3
Average (±1 SD)	54.6 ± 12.5		**16.5 ± 15.1**			0.50 ± 0.21	0.75 ± 0.2	0.76 ± 0.24						21.3 ± 18.6	12.5 ± 11.6	8.8 ± 7.1

Abbreviations: cVEMPs, cervical vestibular-evoked myogenic potentials; CVN, combined vestibular neuropathy; f, female; m, male; NA, not available; oVEMPs, ocular vestibular-evoked myogenic potentials; SCC, semicircular canal; SVN, superior vestibular neuropathy; vHIT, video Head Impulse Test; VSS-AA, Anxiety and Autonomic part of VSS; VSS-VER, vertigo part of VSS; VSS, Yardley Vertigo Symptom Scale.

[a] Bold values indicate significant reduction in gain according to the cut-offs provided in the methods section.

[*] Substantially increased correction saccades consistent with SCC hypofunction despite gain values within normal range.

[†] Status post surgical resection of vestibular schwannoma 2 years and 8 months ago.

[‡] Vestibular schwannoma, status post radiation therapy 4 years ago.

diagnosis of SVN. Impairment of all three semicircular canals accompanied by impaired utricular and saccular function on the same side was mandatory to meet diagnostic criteria for CVN. Only patients with confirmed peripheral–vestibular hypofunction matching SVN or CVN were included, while for controls normal vestibular function was mandatory.

All recordings were obtained on a three-axis, motor-driven turntable system (Acutronic, Jona, Switzerland) that is able to rotate human subjects about any axis in space with a position resolution of 0.01°. Subjects were secured by a five-point belt system. Bolstering the participant's shoulders and knees with pillows minimized body movements and thereby reduced changes in proprioception. While sitting upright, the participant's head was restrained in a straight-ahead upright position with a thermoplastic mask (Sinmed, Reeuwijk, The Netherlands). All experiments were performed in complete darkness. A red arrow (length = 500 mm; width = 3 mm) projected from a turntable-fixed laser onto the center of a sphere 1.5 m away from the subject, was used to indicate perceived visual vertical.

2.3. Experimental paradigm

Participants were asked to rotate the arrow along the shortest path possible using a knob on a remote-control box and to confirm adjustments with a button press. A time limit of 15 s was implemented to minimize risk for adaptation (Tarnutzer et al., 2012b). In total, 120 trials were collected per subject. The arrow starting position deviated pseudo-randomly between 28° and 72° clockwise (CW) or counter-clockwise (CCW), as illustrated in the inset of Fig. 1C. Five different whole-body roll positions were studied (upright, ±45°, ±90°) and after each trial the turntable roll position was changed in a pseudo-random order. Turntable roll acceleration and deceleration was ±10°/s^2. Presentation of the arrow was delayed by 10 s after the turntable reached the testing position in order to allow residual SCC-stimulation to disappear (Jaggi-Schwarz and Hess, 2003). For static SVV adjustments as used here we have previously checked for postrotary torsional ocular drift and nystagmus to quantify the contribution of SCC-stimulation after the movement. We showed that average torsional eye velocity at the time subjects confirmed arrow adjustments was very small (0.10 ± 0.06°/s) (Tarnutzer et al., 2009b).

All participants completed the Yardley Vertigo Symptom Scale (VSS), which assesses the frequency of dizziness/vertigo, imbalance and related autonomic symptoms within the past 12 months. Two subscales differentiate between symptoms associated with vertigo and imbalance (VSS-VER) and anxiety or arousal (VSS-AA) (Yardley et al., 1992).

2.4. Data analysis

SVV adjustments within ±2.5° relative to the gravitational vertical are considered normal (Brandt et al., 1994; Pérennou et al., 2008). Results from patients with left- and right-sided lesions were pooled after having mirrored data from patients with left-sided lesions. Roll-tilt right-ear-down thus equates to roll-tilt towards the affected side ("ipsilesional"), whereas left-ear-down roll-tilts are towards the healthy side ("contralesional"). Accuracy (i.e., the degree of veracity as reflected by the mean adjustment error) and precision (i.e., the degree of reproducibility as reflected by the standard deviation (SD)) of SVV adjustments were determined. Outliers (data points differing >3 SDs from the mean) were removed. As our data was normally distributed (using the Jarque–Bera hypothesis test of composite normality, jbtest.m, Matlab 7.0), mean ± 1 SD values were provided when pooling individual data points. Statistical analysis was performed using SPSS 22 (IBM, Armonk, NY, USA). We applied a generalized linear model,

and main effects included the group ($n = 2$; patients vs. controls), the direction of rotation of the arrow ($n = 2$; CW vs. CCW) and turntable position ($n = 5$). Turntable and line orientation signals were processed with interactive programs written in MATLAB™ (MathWorks, Natick, MA, USA). The level of significance was kept at $p = 0.05$, and Fisher's least significant difference (LSD) method was used to correct for multiple comparisons. To study alterations in SVV accuracy over time, data points of all vestibular neuritis patients were plotted against the time since symptom onset. A linear function was fitted using built-in Matlab functions (regress.m), and the goodness-of-fit (R^2-value) was obtained and F-tests were used to determine the significance of drift. Principal component analysis (PCA) was selected to evaluate correlations between dependent variables. This procedure is equivalent to orthogonal linear regression or total least squares, which minimizes the perpendicular distances from the data points to the fitted model (Van Huffel and Vandewalle, 1991). Multiple least square linear regression differs from PCA in that it implies that one variable (i.e., the independent variable) is known without error. Conversely, PCA appropriately adjusts for errors along all axes. As a measure of the goodness of fit we provided the R^2-value. To estimate the sampling distribution of the slope of the fit obtained by PCA, we used bootstrapping to construct 1000 resamples and calculated the 95%-confidence-interval (CI). A correlation between the two dependent variables was considered significant whenever the 95%-CI of the slope did not include zero.

3. Results

From the 13 patients included, nine met diagnostic criteria for CNV, while four received a diagnosis of SVN. On video-head-impulse testing, reductions in gain were most pronounced for the horizontal canals. For the vertical canals, deficits were less obvious with gains often normal and with only corrective saccades as an indicator of peripheral–vestibular hypofunction (marked with '*' in Table 1). In all patients with SVN and in seven out of nine patients with CVN, oVEMP responses ipsilesionally were absent, indicating complete loss of utricular function on the affected side. In those patients with CVN, cVEMP responses were absent in three, while they were only reduced in the remaining six.

3.1. Accuracy of SVV adjustments

Data from a typical patient with chronic UVH after right-sided SVN is shown in Fig. 1, demonstrating preserved saccular function (cVEMPs: AR = 23%) while utricular function is unilaterally absent and the SVV is shifted ipsilesionally when roll-tilted to the affected side and while upright. When pooling all subjects (patients and controls), there was no main effect for direction of arrow rotation on adjustment errors (df = 1, chi-square = 0.711, $p = 0.399$), so trials with CW and CCW arrow adjustments were pooled for further analyses.

Compared to controls, both the SVN and the CVN group showed significant shifts in adjustments towards the affected side when roll-tilted ipsilesionally (Table 2 and Fig. 2A). While there was a main effect for the lesion pattern (controls vs. CVN vs. SVN, df = 2, chi-square = 6.377, $p = 0.041$) on adjustment errors, pairwise comparison demonstrated a significant difference between CVN patients and controls ($p = 0.029$), while only a trend was found for SVN patients vs. controls ($p = 0.073$). Since no differences between SVN and CVN patients ($p = 0.870$) were observed, they were pooled for further analyses. Comparing adjustment errors in all 13 patients and the controls, a main effect for the group (df = 1, chi-square = 6.552, $p \leqslant 0.001$) and the turntable position (df = 4, chi-square = 530.697, $p < 0.001$) and an interaction between both parameters (df = 4, chi-square = 26.810, $p < 0.001$) was found. Pairwise comparisons between both groups demonstrated significant shifts in adjustment errors towards the affected side at 45° roll ipsilesional ($p < 0.001$) and 90° roll ipsilesional ($p = 0.003$), while in upright position only a trend was observed ($p = 0.099$). No significant differences in SVV adjustments were observed for contralesionally roll-tilted positions (Table 2).

We noted smaller adjustment errors for patients with reduced oVEMP responses on the ipsilesional side compared to those with ipsilesionally absent oVEMPs (Fig. 2B). However, due to the small number of patients with partial utricular loss ($n = 2$) we did not perform any statistical analyses for these subgroups.

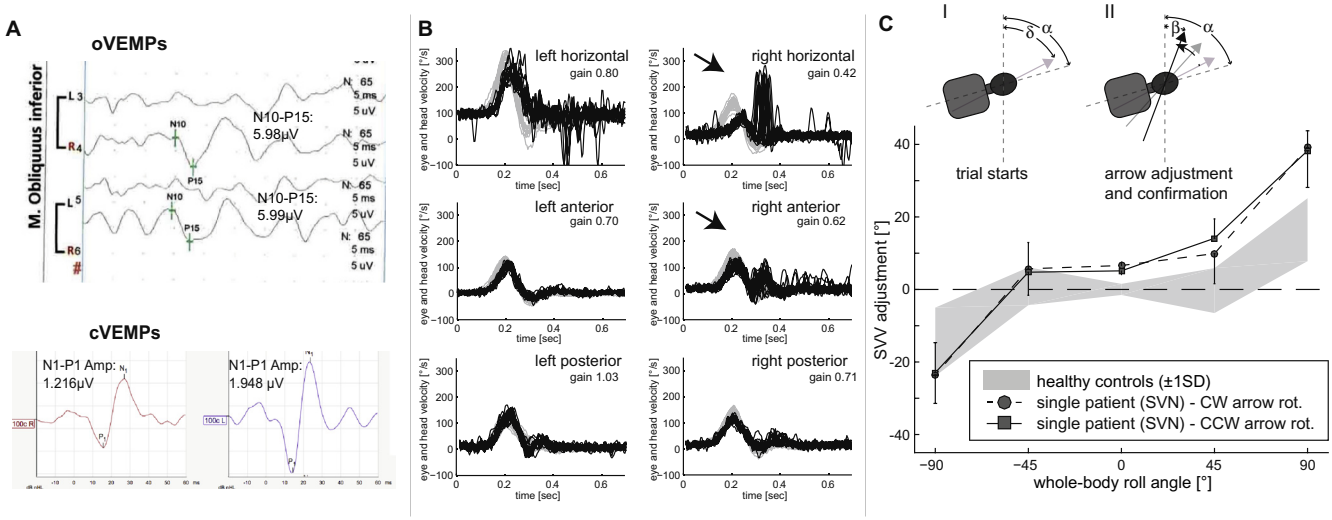

Fig. 1. Single subject data from a patient (#12) with a history of right-sided vestibular neuropathy. (A) Absent oVEMPs and preserved cVEMPs (non-significant asymmetry of 23%) on the affected side, as well as (B) pathologic gains in right horizontal (0.42) and right anterior (0.62) SCC indicate chronic UVH restricted to the superior branch of the vestibular nerve. (C) When roll-tilted towards the healthy side, SVV adjustments were not different from those of the healthy control group. However, whole-body roll-tilts towards the affected side resulted in an increased errors when roll-tilted to the right side. The inset illustrates a single trial with the subject roll-tilted by angle α to the right side at trial onset (I) with the arrow deviating by angle δ from earth-vertical. After completing the arrow adjustment (II), the angle β between perceived vertical and earth-vertical refers to the adjustment error.

3.1.1. Impact of complete ipsilesional loss of utricular function on adjustment errors

When restricting our analysis to patients with ipsilesionally *absent* oVEMP responses ($n = 11$) and controls, we noted a main effect for turntable positions (df = 4, chi-square = 541.901, $p < 0.001$) and for the two groups (df = 1, chi-square = 7.085, $p = 0.008$). A significant interaction between the groups and the turntable position was noted (df = 4, chi-square = 37.121, $p < 0.001$). Pairwise comparisons demonstrated significant shifts in the patients when roll-tilted 45° and 90° ipsilesionally and when roll-tilted 90° contralesionally (Table 2).

3.2. SVV trial-to-trial variability

Like the controls, patients showed a v-shaped pattern of variability with a local minimum in upright position and increasing values with increasing roll-tilt. Statistical analysis showed a main effect for the group (patients vs. controls; df = 1, chi-square = 10.668, $p = 0.001$) and the turntable position (df = 4, chi-square = 145.014, $p < 0.001$), while no significant interactions were noted. Compared to upright, variability in all roll-tilted positions was significantly ($p < 0.001$) increased. Pairwise comparisons demonstrated a significant increase in variability for the patients compared to the controls at 90° roll contralesional ($p = 0.001$), while in all other positions no differences were found. There was a main effect for the lesion pattern (CVN vs. SVN vs. controls; df = 2, chi-square = 19.968, $p < 0.001$) with variability being significantly larger for patients with CVN compared to SVN ($p = 0.044$) and controls ($p < 0.001$), while no significant difference in variability was found for SVN patients and controls ($p = 0.256$) (Fig. 2C, Table 3). We noted overall larger trial-to-trial variability for patients with unilaterally absent oVEMP-responses compared to those with reduced responses on oVEMPs (Fig. 2D). However, due to the small number of patients with partial utricular failure ($n = 2$) we did not perform any statistical analysis for these subgroups.

3.2.1. Impact of complete ipsilesional loss of utricular function on trial-to-trial variability

When restricting our analysis to patients with ipsilesionally *absent* oVEMP responses ($n = 11$) and controls, we noted a main effect for the turntable position (df = 4, chi-square = 142.487, $p < 0.001$) and the two groups (df = 1, chi-square = 17.380, $p < 0.001$), while no significant interactions were noted (df = 4, chi-square = 4.490, $p = 0.344$). Pairwise comparisons demonstrated significantly larger variability for patients with absent oVEMP responses when roll-tilted 90° ipsilesionally ($p = 0.046$) and 90° contralesionally ($p < 0.001$) (Table 3).

3.3. The effect of disease duration

Linear decay functions were fitted on mean errors plotted against disease duration for the different whole-body roll positions separately (Fig. 3). Due to the progressive nature of the disease, patients with vestibular schwannoma ($n = 2$) were excluded from this analysis. A significant linear decrease in errors was noted in upright position (Fig. 3C) and when roll-tilted ipsilesionally (Fig. 3D and E), while for contralesionally roll-tilted positions there is no suggestion of a decrease in errors with time (Fig. 3B), or only a non-significant trend (Fig. 3A).

3.4. Yardley Vertigo Symptom Scale

There was a main effect for the group (df = 2, chi-square = 37.015, $p < 0.001$), while no main effect for the different VSS scores (VSS total, VSS-VER, VSS-AA) was noted (df = 2, chi-square = 0.247, $p = 884$) and no interaction between the two parameters (group and type of VSS score) was observed (Fig. 4). Pairwise comparisons demonstrated higher VSS scores in CVN ($p < 0.001$) and SVN ($p = 0.013$) patients compared to controls and a trend towards higher scores in CVN compared to SVN patients ($p = 0.069$). To further investigate whether subjective complaints may resolve with disease duration or could be associated with the size of adjustment errors, the total VSS score of all patients was correlated to disease duration and adjustment errors in upright position. Again, the two patients with vestibular schwannoma were excluded. Linear regression analysis demonstrated no significant correlation between time since symptom onset and the total VSS score ($R^2 = 0.01$, $p = 0.745$, slope = −0.398 [−3.090–2.293, 95%-CI]). Likewise, PCA showed no correlation between the total VSS score and the size of adjustment errors when upright ($R^2 = 0.52$, slope = 5.91 [−11.64–12.04, 95%-CI]).

4. Discussion

We observed roll-angle dependent shifts in the perceived direction of gravity in our chronic UVH patients. While the SVV was shifted for roll tilts towards the side of the lesion, SVV adjustments while roll-tilted to the contralesional side were not significantly different from those in healthy controls.

In the literature, acutely after UVH a strong bias of the SVV and the subjective visual horizontal (SVH) towards the lesioned side (up to 25° (Friedmann, 1971; Curthoys et al., 1991; Bergenius et al., 1996; Anastasopoulos et al., 1997; Lopez et al., 2008)) has been described consistently. While this bias slowly decreases, not all patients reach normal values after months to years (Friedmann, 1970; Curthoys et al., 1991; Böhmer and Rickenmann, 1995; Tribukait et al., 1998; Hafström et al., 2004;

Table 2
SVV adjustment errors.[a]

Body roll angle	Healthy controls ($n = 17$)	CVN ($n = 9$)		SVN ($n = 4$)		UVH with partial or complete utricular hypofunction (AR > 30%)		UVH with *complete* utricular hypofunction (AR = 100%)	
	Error (°) mean ± 1 SD	Error (°) mean ± 1 SD	*p*-Value*	Error (°) mean ± 1 SD	*p*-Value*	Error (°) mean ± 1 SD	*p*-Value*	Error (°) mean ± 1 SD	*p*-Value*
−90°	−14.9 ± 9.5	−19.2 ± 8.3	0.549	**−22.7 ± 5.3**	**0.019**	−18.5 ± 7.0	0.126	**20.5 ± 7.3**	**0.021**
−45°	0.9 ± 5.4	−2.9 ± 6.6	0.233	−3.7 ± 4.6	0.168	−2.8 ± 5.6	0.130	−3.2 ± 5.9	0. 112
0°	0.0 ± 1.2	3.6 ± 2.2	0.220	4.8 ± 1.8	0.154	*3.7 ± 2.0*	*0.099*	*4.0 ± 2.1*	*0.088*
+45°	−0.2 ± 6.4	**9.6 ± 5.4**	**0.001**	**11.4 ± 4.5**	**0.001**	**9.2 ± 4.8**	**<0.001**	**10.3 ± 5.0**	**<0.001**
+90°	16.8 ± 8.8	**25.1 ± 6.0**	**0.033**	**26.5 ± 5.9**	**0.004**	**23.5 ± 5.7**	**0.003**	**25.6 ± 5.9**	**<0.001**

Abbreviations: AR, asymmetry ratio; CVN, combined vestibular neuropathy; SVN, superior vestibular neuropathy; UVH, unilateral peripheral–vestibular hypofunction.
[a] Values in bold indicate statistically significant differences in SVV adjustments compared to the healthy controls.
* Pairwise statistical analyses (using a generalized linear model) of the patient groups were always against the healthy control group.

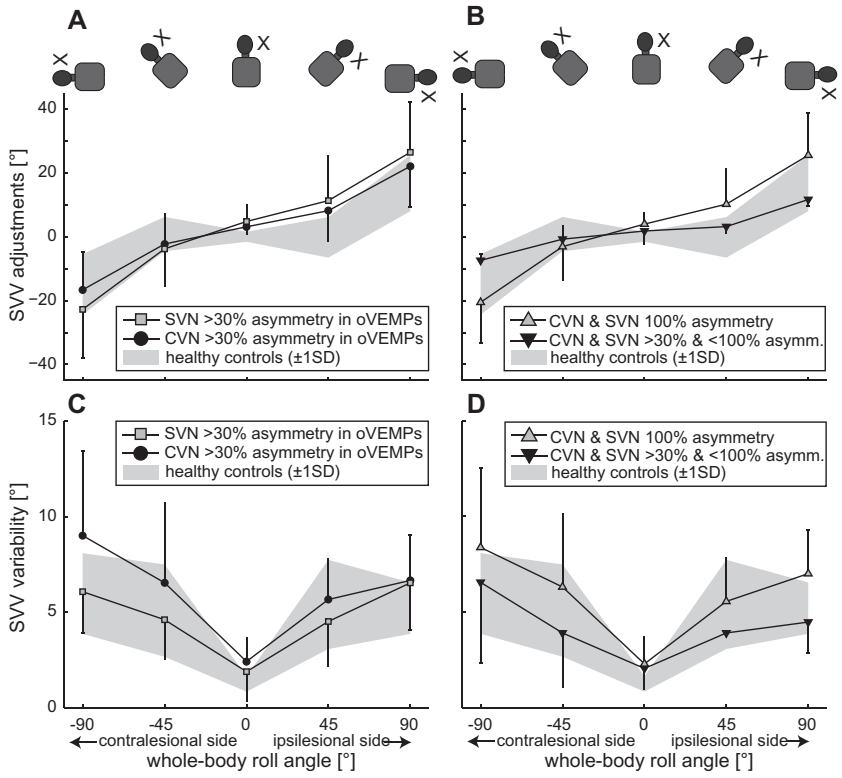

Fig. 2. Illustration of adjustment errors (mean ± 1 SD) and trial-to-trial variability in patients and controls. Since SVV values were mirrored along both the *x*- and *y*-axis for cases with left-sided lesions to allow pooling with right-sided lesions, the affected side is always the right side. Panel A: mean (±1 SD) adjustment errors in patients with CVN (black circles) and SVN (grey squares) are compared to the results from controls (grey-shaded area = ±1 SD), showing a very similar pattern in both patient populations. Panel B: Comparison of mean adjustment errors in patients with partial (black inverted triangles) and complete (grey triangles) utricular loss as assessed by oVEMPs (CVN and SVN pooled), demonstrating significant shifts only in the patients with complete utricular loss. Panel C: Mean trial-to-trial variability of patients with CVN (black circles) and SVN (grey squares) compared to results from healthy controls (grey-shaded area = ± 1 SD). The SVN group included only patients with complete utricular loss. Panel D: Mean trial-to-trial variability of patients with partial (black inverted triangles) and complete (grey triangles) utricular loss compared to healthy controls. Note that patients with CVN and SVN were pooled, however, all SVN patients had complete utricular loss on the affected side. Insets indicate the subject's whole-body roll orientation (as seen from behind) for the different conditions and an 'x' indicates the side with vestibular hypofunction which was by definition the right side. Abbreviations: CVN, combined vestibular neuropathy; SD, standard deviation; SVN, superior vestibular neuropathy; SVV, subjective visual vertical.

Table 3
SVV trial-to-trial variability.[a]

Body roll tilt angle	Healthy controls (*n* = 17)	CVN (*n* = 9)		SVN (*n* = 4)		UVH with partial or complete utricular hypofunction (i.e., asymmetry > 30%) (*n* = 13)		UVH with *complete* utricular hypofunction (i.e., asymmetry = 100%) (*n* = 11)	
	Variability (°) mean ± 1 SD	Variability (°) mean ± 1 SD	*p*-Value*	Variability (°) mean ± 1 SD	*p*-Value*	Variability (°) mean ± 1 SD	*p*-Value*	Variability (°) mean ± 1 SD	*p*-Value*
−90°	6.0 ± 2.1	**9.0 ± 4.4**	**<0.001**	6.1 ± 2.2	0.884	**8.1 ± 4.0**	**0.002**	**8.4 ± 4.1**	**<0.001**
−45°	5.1 ± 2.4	7.0 ± 4.4	0.109	4.6 ± 2.1	0.957	6.2 ± 3.9	0.302	*6.7 ± 4.1*	*0.099*
0°	1.2 ± 0.4	2.4 ± 1.3	0.121	1.9 ± 1.6	0.112	2.3 ± 1.3	0.141	2.3 ± 1.4	0.141
+45°	5.4 ± 2.3	5.7 ± 2.1	0.491	4.5 ± 2.3	0.893	5.3 ± 2.1	0.795	5.6 ± 2.2	0.501
+90°	5.2 ± 1.3	6.7 ± 2.4	0.077	6.5 ± 2.5	0.103	6.6 ± 2.3	0.132	**7.0 ± 2.3**	**0.046**

Abbreviations: CVN, combined vestibular neuropathy; SVN, superior vestibular neuropathy; UVH, unilateral peripheral-vestibular hypofunction.
[a] Values in bold indicate statistically significant differences in SVV variability compared to the healthy controls.
* Pairwise statistical analyses (using a generalized linear model) of the patient groups were always against the healthy control group.

Hafstrom et al., 2006; Lopez et al., 2008; Toupet et al., 2014), with adjustment errors between −2.0° and 11.7°. These results are consistent with our observation of a trend (3.7 ± 2.0°, $p = 0.100$) towards an ipsilesional SVV bias when upright.

Adjustment errors in the roll plane were asymmetric in our patients, rejecting the hypothesis that a constant offset is added to physiological deviations in SVV adjustments when roll-tilted. Moreover, our results support the hypothesis of roll-angle dependent errors that are significantly more pronounced for ipsilesionally roll-tilted positions (Tarnutzer et al., 2011b). The utricular organs have been described as asymmetric sensors with a preference for ipsilateral roll-tilt (Dai et al., 1989). Due to the relatively larger ipsilateral utricular contribution, unilateral utricular hypofunction may become apparent when roll-tilted to the affected side rather than when roll-tilted to the healthy side. If one utricle is lost, the remaining one has been proposed to become bidirectionally sensitive within six to ten weeks (Lempert et al., 1998). Persistent shifts in SVV when ipsilesionally roll-tilted may, thus, indicate insufficient adaptation of utricular sensitivity to ipsilesional roll-tilt. This may affect verticality perception in two different ways:

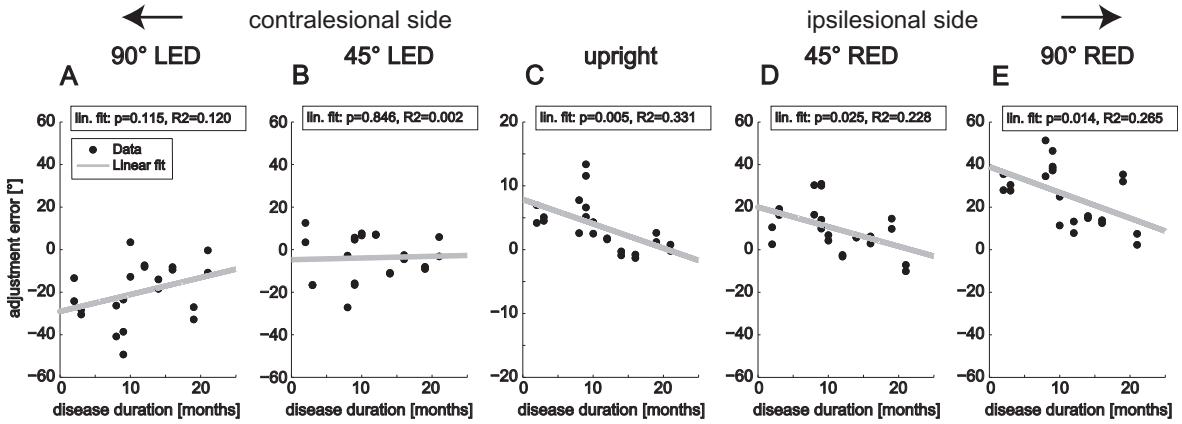

Fig. 3. Relationship between disease duration and adjustment errors in UVH patients. Individual mean adjustment errors (trials with CW and CCW arrow rotation shown separately) were plotted against disease duration (in months) for all roll-angles tested (0°, ±45°, and ±90°) and linear fits were applied. Statistical results of fitting are shown in insets. Data from patients with left-sided UVH was mirrored to allow pooling with data from right-sided UVH cases. By definition, the vestibular hypofunction was on the right side. Note that the two patients with vestibular schwannoma were excluded from this part of the analysis.

(1) imbalanced otolithic input causes an erroneous internal estimate of direction of gravity or (2) pathological ocular torsion resulting from a lateralized disturbance in the vestibulo–ocular pathways results in a roll-tilt of the visual environment (Curthoys et al., 1991; Dieterich and Brandt, 1992; Tarnutzer et al., 2009b). Anecdotal observations in patients with acute vestibular nuclear lesions favor the latter mechanism. In these cases the subjective haptic vertical (which does not rely on retinal input and therefore is not affected by ocular torsion) remained accurate while the SVV was strongly biased (Bronstein et al., 2003). However, assuming a link between ocular torsion and the SVV, asymmetric ocular torsion for ipsilesional and contralesional roll-tilts is predicted. To our knowledge, this hypothesis has not been investigated. Nevertheless, the perception of gravity seems to contribute to errors when upright, since SVV roll-tilts have been observed in patients with central lesions along the vestibular pathways that left the vestibulo–ocular pathways unaffected (Baier et al., 2012).

Average adjustment errors when roll-tilted towards the healthy side are larger than average values for the healthy controls in these positions, which could be explained by the concept of prior knowledge in Bayesian optimal observer models (Knill and Pouget, 2004; Kording and Wolpert, 2004). According to these models, the brain assumes that small body-roll angles are most likely (De Vrijer et al., 2008). If current vestibular and extra-vestibular graviceptive input becomes less reliable, prior knowledge is weighted more (De Vrijer et al., 2008). Since the prior is aligned with the body-longitudinal axis, this will shift perceived vertical away from earth-vertical (Tarnutzer et al., 2010). Noteworthy, when restricting the analysis to patients with absent oVEMP responses, errors while roll-tilted 90° towards the healthy side were significantly larger than in the controls (Fig. 2B). However, observed shifts in patients were about twice as large when roll-tilted towards the affected side. Potentially, the increase in adjustment errors on both ipsilesional and contralesional sides may be related to increased weighting of the prior in patients. However, to explain the larger shifts on the ipsilesional side, an asymmetric increase in the weight of the prior would be required.

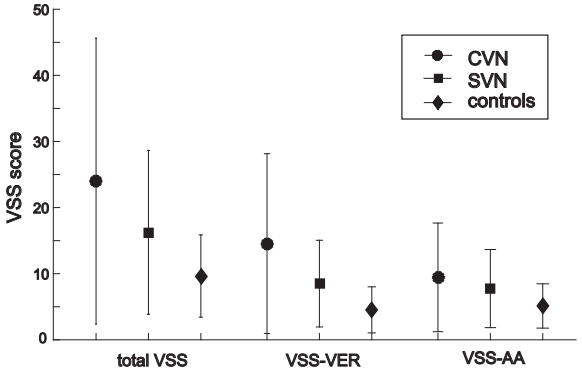

Fig. 4. Mean (±1 SD) VSS scores of the 13 patients with CVN and SVN compared to the healthy controls. Abbreviations: VSS, vertigo symptom scale; VSS-AA, Anxiety and Autonomic part of VSS; VSS-VER, vertigo part of VSS; CVN, combined vestibular neuropathy; SVN, superior vestibular neuropathy.

Few studies have looked at the SVV or SVH while roll-tilted in patients with UVH (Dai et al., 1989; Böhmer and Rickenmann, 1995; Bergenius et al., 1996; Betts et al., 2000). In the acute stage when upright and when roll-tilted 30° towards the affected side, adjustments were biased ipsilesionally by 8.9° (Bergenius et al., 1996), while for 30° roll-tilt towards the healthy side, errors were small (<2.0°). Over the course of 11 weeks, the ipsilesional bias decreased and values for upright (2.2°) and 30° roll-tilt towards the affected ear (3.5°) were of similar size while no errors for contralesional roll were found (Bergenius et al., 1996). Acutely after vestibular neurectomy, Böhmer and Rickenbach observed a larger bias when patients were roll-tilted 90° towards the affected ear than towards the healthy ear (Böhmer and Rickenmann, 1995), while errors normalized after six months in this case series. Using a centrifuge, a roll-tilt stimulus angle of 26° was applied by Dai, demonstrating roll under-compensation when roll-tilted ipsilesionally and roll over-compensation when roll-tilted away from the affected side in the acute stage. While results for a roll-tilt stimulus angle of 26° normalized for the healthy side, roll under-compensation persisted on the affected side after 24 weeks, yielding values of 9.3 ± 3.6° (Dai et al., 1989). In summary, both the size of the A-effect at small roll angles (45°) and the asymmetric pattern of errors in our chronic UVH patients are consistent with observations in the literature.

4.1. SVV accuracy in patients with different patterns of peripheral–vestibular hypofunction

Since SVV accuracy in CVN and SVN patients did not differ significantly, saccular input seems to be of minor importance for the perception of gravity over the range of roll-angles studied. Likewise, normal adjustments were reported in all but one patient with

isolated inferior vestibular neuritis in upright position (Kim and Kim, 2012). The extent of utricular deficiency seems to influence verticality perception as well: patients with partial utricular failure demonstrated smaller errors than patients with complete utricular loss. However, the number of cases with partial utricular failure was too small to allow statistical analysis.

4.2. Changes of SVV accuracy over time

Previous studies described smaller errors when upright one year after disease-onset (Dai et al., 1989; Bergenius et al., 1996). We found a significant linear decay of errors in upright position and in ipsilesionally roll-tilt positions. Whether, in an extended period of observation, linear approximation still fits appropriately when describing the course of adjustment errors than the exponential function, remains open. Since we did not consider any vestibular neuritis patients until they were chronic (i.e., at least three months after onset), early compensatory mechanisms are not reflected in our data. The observation that ipsilesional offset further declines in chronic patients suggests long-term ongoing compensatory mechanisms.

4.3. SVV precision

Previous studies reported that trial-to-trial variability in healthy controls grows with increasing roll-angle (De Vrijer et al., 2008; Tarnutzer et al., 2009a). This was confirmed in our study and also observed in the patients. UVH resulted not only in changes in SVV accuracy, but also affected the precision of SVV adjustments. Specifically, the lesion pattern (SVN vs. CVN) had an impact on SVV precision. The significantly higher variability in cases with combined utricular and saccular damage compared to isolated utricular involvement supports the hypothesis that both the utriculus and the sacculus contribute to precise verticality estimates and that the brain can deal with the loss of a single utriculus, keeping SVV estimates as precise as in healthy controls.

4.4. Subjective judgment of vertigo/dizziness

Although complaints in patients with UVH generally improve within days to few weeks, VSS scores were significantly higher in our UVH patients than in the healthy controls, reflecting imperfect compensation. No correlation between the total VSS score in patients and adjustment errors when upright was observed, putting the functional relevance of such improvements into question. This discrepancy is in agreement with a previous report showing lack of correlation between SCC function after vestibular neuritis and subjective complaints (Palla et al., 2008).

5. Conclusions

Deficiencies in verticality perception seem lateralized in chronic UVH, and insufficient adaptation of the contralesional utricle's sensitivity to ipsilesional roll-tilt may explain this pattern. Comparable patterns of SVV adjustments in CVN and SVN suggest a dominant role of utricular input for accurate verticality perception. However, saccular input may be important as well to improve precision. With shifts in perceived vertical being restricted to roll-tilted positions, obtaining SVV measurements while roll-tilted may help identify those patients that suffer from persistent UVH and who could benefit from targeted balance training.

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