

Verticality perception in patients with lesions along the graviceptive pathways

Acute deficits and subsequent compensation

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Summary

Bilateral central vestibular pathways (CVP) send signals from the vestibular nuclei to the cerebellar, brainstem, and cortical areas that are involved in processing graviceptive signals. Whereas the estimated direction of gravity is accurate when upright, systematic angle-dependent errors can occur when roll-tilted: over-estimations at small and very large roll angles (E-effect) and roll under-estimation at medium-sized roll angles (A-effect). Acute lesions along the CVP frequently lead to deviations of the subjective visual vertical (SVV). Whereas SVV errors in upright positions have been well characterised, changes in the A- and E-effect and in SVV precision due to lesions along the CVP have not been studied in roll-tilted positions. We report on a series of patients with CVP lesions and compare SVV measurements in different roll orientations (0° , $\pm 45^\circ$, $\pm 90^\circ$) in the sub-acute state (4–33d) with follow-up ~4 months later. In an upright position, 5/6 patients showed SVV deviations in the sub-acute state; in 3 patients deviations were ipsilesional. When roll-tilted, 4/6 patients showed increased SVV errors. In all patients, the pattern of SVV errors could be explained by combining an SVV offset in an upright position with body-position-dependent errors when roll-tilted, being larger on the ipsilesional side and smaller on the contralesional side or vice versa. SVV precision was decreased in 4 patients. After 4 months, verticality perception was either improved ($n = 1$) or within normal range ($n = 2$) in terms of accuracy and precision in 3/4 patients. These results show that lesions along the CVP result in altered estimates of the direction of gravity in the entire roll plane, which can improve within a few months due to central compensation. At the time, accuracy had normalised in upright positions, estimated direction of gravity when roll-tilted could still be erroneous. Assessing the SVV in roll-tilted positions may reveal more subtle deficiencies and may hence support continuation of balance physiotherapy.

Key words: vestibular; otolith organs; perception; subjective visual vertical

Introduction

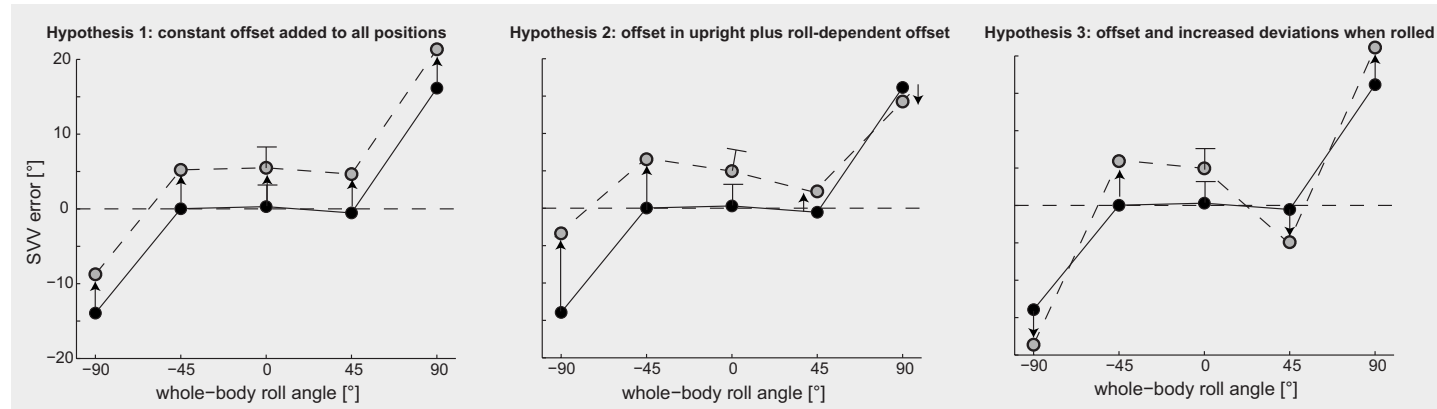
The central vestibular pathways (CVP) interconnect a network of the brainstem, cerebellar, thalamic and cortical areas involved in the processing, integration, and perception of “graviceptive” input [1, 2]. Otolith and semicircular canal (SCC) inputs converge at the vestibular nuclei [3], project via bilateral ascending pathways through the medial lateral fascicle (MLF) to the interstitial nucleus of Cajal (INC) and to the posterolateral thalamus [4], and end in the temporo-peri-Sylvian vestibular cortex (TPSVC). The TPSVC is considered to be the human analogue of the parieto-insular vestibular cortex (PIVC) in non-human primates [5], where the vestibular input converges with other sensory signals and sub-serves perception of spatial orientation and navigation [6]. In the upright position, the internal representation of gravity and spontaneous head orientation aligns with gravity, while the torsional orientation of the eyes is symmetric (binocular fundoscopic torsion = 0°). Depending on the exact topography of the lesion, vestibular tone-imbalances lead to roll tilts of perception, head, and body as well as to misalignments of the visual axes (skew deviation) [7, 8] and binocular torsion [1].

Perception of self orientation relative to gravity can be assessed by aligning an illuminated line with the perceived vertical, termed the “subjective visual vertical” (SVV) [9]. Under static conditions in darkness, the SVV is mainly influenced by otolith signals. Estimates of SVV in upright positions are accurate (i.e., within a range of $\pm 2^\circ$, [9, 10]). Aligning a luminous line to the perceived vertical while roll-tilted requires the subject to compensate for body roll. Body roll leads to errors towards over-estimation (E-effect) at moderate roll angles up to 60° [11–13], whereas at roll angles larger than 60° perceived body roll is biased towards under-estimation (A-effect) [12, 14]. It was suggested that A- and E-effects are a consequence of how various sensory signals are integrated into a unified perception of vertical [14]. While Mittelstaedt put a focus on an imbalanced otolith input to cause the A- and E-effects [14], more recent modelling of perceived vertical underlined the role of a noisy but accurate otolith signal [13, 15]. To maximise the precision of verticality estimates, this noisy otolith estimate is combined with a bias that represents prior knowledge about where vertical is located. This bias refers to the body-longitudinal axis and is based on the assumption that small roll-

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Figure 1

In this figure, distinct hypothetical changes in perceived vertical in both upright and roll-tilted positions are illustrated (grey circles). For comparison, average SVV adjustments from healthy normal subjects (in black) are shown. Whereas hypothesis 1 suggests a constant offset of SVV over the entire roll plane, hypothesis 2 proposes body-position-dependent SVV errors in roll-tilted positions that are in the same direction (shown) or in the opposite direction (not shown) as the offset of SVV in the upright position. Alternatively, lesions along the CVP may increase the noise in the sensory estimate and cause not only a shift of SVV in upright but increase the error signal, so that both established A- and E-effects would become larger (hypothesis 3).



tilt angles are more likely than large angles. Using this modelling approach, verticality estimates at small roll angles are accurate and precise, however, at larger roll angles, both A- and E-effects arise, reflecting the experimental data well [13, 15].

Following unilateral or bilateral lesions along the CVP, the SVV becomes biased and increased noise levels of the centrally obtained estimate of vertical will interfere with the A- and E-effect. However, little is known about the interaction between the A- and E-effect and shifts caused by lesions along the CVP. Hypothetically, various changes in the pattern of A- and E-effects may emerge. The most straight forward hypothesis is that an imbalance of the graviceptive input is combined additively with the physiological deviations when roll-tilted, resulting in a *constant offset* of the A- and E-effect over the entire roll plane (hypothesis 1). Alternatively, shifts in SVV in an upright position may be accompanied by body-position-dependent errors in the direction or in opposite direction of the SVV offset in an upright position. Thereby E-effects would become more pronounced and A-effects would decrease (hypothesis 2), or vice versa (not shown). Overall, shifts in the SVV may result in larger A- and E-effects as the noise level of the graviceptive signal is likely to be larger. Under these circumstances, the brain might put more weight on prior knowledge at the cost of *increased SVV errors* at larger roll angles (hypothesis 3).

In patients with acute lesions along the CVP, verticality perception has been studied in upright positions only. Whereas peripheral vestibular [16–19] and caudal brainstem lesions resulted in ipsiversive tilts of SVV, more rostral brainstem lesions yield contraversive SVV deviations [20]. Contraversive SVV tilts and contraversive signs of ocular tilt reaction (OTR; consisting of ocular torsion, skew deviation and head-tilt) in patients with acute cerebellar stroke have been related to either nodular [21] or dentate nucleus lesions [22], whereas in patients with ipsiversive SVV tilts and ipsiversive OTR the dentate nucleus was spared and lesions were located in the biventer lobule, the middle cerebellar peduncle, the tonsil and the inferior semilunar

lobule [22]. Acute lesions within the territory of the middle cerebral artery including the posterior part of the insula, the insular gyrus, and the middle and superior temporal gyrus yielded mostly contraversive SVV tilts and imbalance of gait [23]. Ipsiversive SVV tilts and impaired postural stability were reported in a patient with a metastasis extending from the superior temporal gyrus to the first long insular gyrus [24], suggesting involvement of the superior temporal gyrus in estimating gravity. Here we evaluated both the accuracy and precision of SVV adjustments in patients with lesions along the CVP in various roll-tilted positions, both in the sub-acute and the chronic state, to further characterise 1) the pattern of A- and E-effects when the graviceptive input is imbalanced and 2) recovery of verticality perception, both in terms of accuracy and precision. Based on the literature, it was hypothesised that both the pattern of roll over- and under-estimation and precision are altered in the patients.

Methods

Subjects

We report on a series of patients with acute ischemic or haemorrhagic lesions along the CVP, treated at the Department of Neurology at the University Hospital Zurich between November 2007 and December 2008, and compare measurements in the sub-acute stage with a follow-up ~4 months later (obtained in 4 out of 6 patients). Inclusion criteria were clinical findings suggestive of an acute lesion along the CVP (e.g., spontaneous or gaze-evoked nystagmus, partial or complete ocular tilt reaction, gait ataxia, dysmetria) or neuro-imaging findings suggestive of an affliction of the CVP. The locations of the lesions are described in the single cases. Informed written consent from all subjects was obtained after a full explanation of the experimental procedure. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki for research involving human subjects.

Experimental setup

In all patients, a careful neuro-ophthalmological and neuro-otological examination was performed and magnetic resonance imaging (MRI) including Flair, T2- and diffusion-weighted imaging (DWI) was obtained. SVV adjustments were collected on a motor-driven turntable (Acutronic, Jona, Switzerland). Subjects were secured with a 4-point safety belt and the head was positioned and fixed viewing straight ahead with a thermoplastic mask. Five whole-body roll orientations were studied: upright, 45° right-ear down (RED), 90° RED, 45° left-ear down (LED), and 90° LED. A remote control box allowed the subjects to rotate an arrow projected on a sphere in front and to confirm adjustments. The arrow projection started 10 seconds after the turntable came to a full stop. The arrow starting position deviated pseudo-randomly between 28 and 72° clockwise (CW) or counter-clockwise (CCW). Subjects were instructed to adjust the arrow along the perceived gravitational vertical (gravicentrically) in otherwise complete darkness within 15 seconds. After a training session, each trial type was run 24 times, resulting in a total of 120 trials, recorded in a single session. For static SVV adjustments as used here, we have previously checked for post-rotary torsional ocular drift and nystagmus to quantify the contribution of SCC stimulation after the movement and showed that average torsional eye velocity at the time that subjects confirmed arrow adjustments was small ($0.10 \pm 0.06^\circ/\text{s}$) [25]. For comparison, we considered SVV adjustments previously obtained from a group of seven healthy normal subjects using a similar paradigm [15].

Data analysis

SVV adjustment outliers were defined as data points differing more than three standard deviations (SD) from the mean. In total, less than 0.1% of all trials were discarded. Average deviations relative to earth-vertical and the SD were calculated for each subject. CW deviations relative to earth-vertical have a positive sign. In the following, we will use the term “trial-to-trial variability” whenever we report intra-individual SD. One of the co-authors, an experienced neuroradiologist (BS), delineated the location and extension of the lesions and the exact involvement of the CVP on all MRI sequences obtained.

Results

Description of single cases

Patient 1 (DD)

This 33-year-old male patient presented with slurred speech, acute right hemiataxia, and gait deviation to the right. No spontaneous or direction-changing horizontal nystagmus was noted, pursuit was smooth and saccades were metric. With MR-imaging, right cerebellar ischemia in the territory of the superior cerebellar artery (SCA) affecting the right superior cerebellar peduncle, the biventer lobe and the inferior semilunar lobe, but sparing the nodulus, the dentate nucleus and midbrain structures was found. In the sub-

acute stage (recorded 10 days after initial symptoms), the SVV was tilted ipsilesionally (i.e., CW) by 5.4° on average when upright. In all roll-tilted positions, roll over-estimation (E-effect) was observed, however, deviations were clearly larger for LED positions compared to RED positions. In the follow-up, recovery was noted and SVV estimates in upright position were accurate. In roll-tilted positions, SVV deviations were symmetric (RED vs. LED) and consistent with the literature (variable E-effects at small roll angles, A-effects at roll angles >60° ear-down). Overall, this patient showed a tendency towards roll over-estimation in all roll-tilted positions. Trial-to-trial variability in both the sub-acute and the chronic stage was not affected and resembled the pattern observed in the control subjects.

Patient 2 (EW)

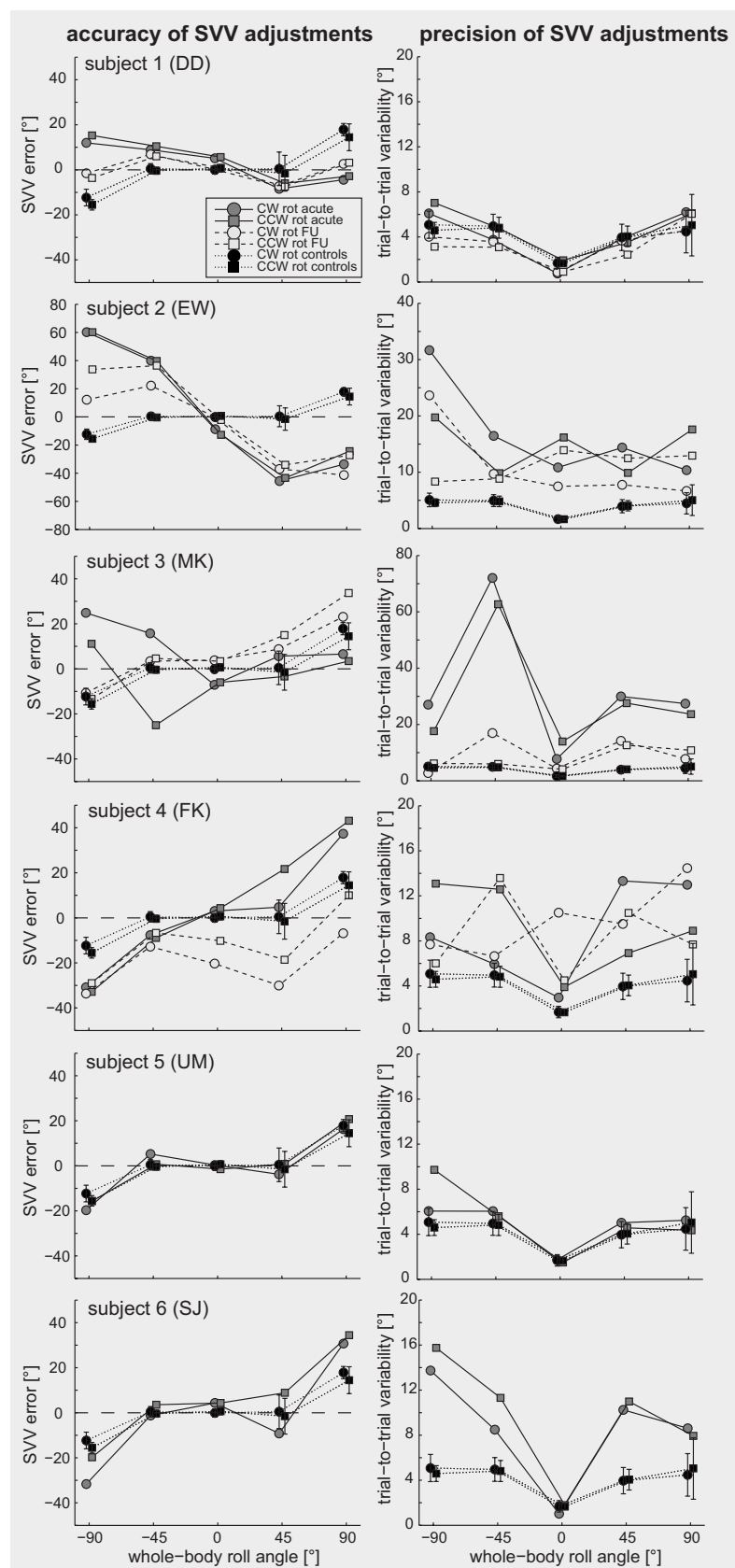
This 66-year-old male patient presented with acute dysarthria, right-sided dysmetria, direction-changing horizontal nystagmus, and gait ataxia. MR-imaging showed a right cerebellar haemorrhage involving the brachium pontis, the dentate nucleus and the superior cerebellar peduncle on the right side. SVV adjustments (obtained 5 days after onset of symptoms) showed an average contralesional (i.e., CCW) tilt of SVV (-10.7°) in an upright position. In all roll-tilted positions, large roll over-compensation with deviations up to 60° were noted. In the follow-up, SVV in the upright position was accurate and slightly reduced, but still considerably large E-effects persisted after 4 months in all roll-tilted positions. Trial-to-trial variability was increased in all roll positions studied in the sub-acute stage. The roll-angle dependent modulation of SVV variability (yielding increasing values with increasing roll angle), however, was reduced. Compared to the sub-acute stage, variability was slightly reduced in the follow-up, however, remained clearly larger than the healthy controls.

Patient 3 (MK)

This 65-year-old male patient presented with vertical gaze palsy, slow upward saccades, abolished downward saccades, missing torsional quick-phases when tilting the head to the right, hypophonia, hypersomnia and right hemiataxia. MR-imaging yielded a paramedian central thalamic lesion on the left side and a paramedian rostral thalamic lesion on the right side. On the left side, the lesion expanded into the midbrain affecting the medial longitudinal fasciculus (MLF) and the interstitial nucleus of Cajal (INC). SVV adjustments (obtained 19 days after onset of symptoms) yielded an average CCW tilt (-6.5°) in the upright position, which was ipsilateral to the left paramedian mesencephalic lesion. In roll-tilted positions, under-compensation was either reduced (in 90° RED) or inversed, now yielding roll over-compensation (90° LED). In the follow-up, the pattern of SVV changed: now an average offset of 3.6° into CW direction while being upright was found and in roll-tilted positions, SVV adjustments were shifted CW relative to the healthy control subjects. This shift was larger for RED roll-tilts. Trial-to-trial variability was several fold increased in the sub-acute stage (being most prominent in 45° LED position) and partially normalised after ~4 months, however, remained at a clearly larger level than in the control subjects.

Figure 2

Single subject average SVV errors (left column) and trial-to-trial SVV variability (right column) are plotted against whole-body roll angle, both in the sub-acute stage (in dark grey) and for the follow-up (FU) ~4 months later (in light grey). Trials with CW (circles) and CCW (squares) arrow rotations are shown separately. For comparison, average (± 1 SD) SVV errors and variability values from healthy control subjects [15] are shown (in black). Note that the scaling on the ordinate for the SVV accuracy (subject 2) and SVV precision (subjects 2 and 3) is different.

**Patient 4 (FK)**

This 65-year-old male patient presented with horizontal gaze palsy, impaired upgaze, left trigeminal hypesthesia, and left-sided sensorimotor impairment. With initial MR-imaging, a predominantly right-sided ponto-mesencephalic dorsal haemorrhage was found, involving the medial vestibular nuclei bilaterally, the superior and the lateral vestibular nucleus on the right side, the INC on the right side and the MLF on both sides. No cerebellar (e.g., affecting the dentate nucleus or the cerebellar nodulus) or thalamic structures were involved. At follow-up after four months, the patient had newly developed a vertical pendular nystagmus and increasing gait ataxia. Repeated MR-imaging revealed a hypertrophic degeneration of the right inferior olive. SVV adjustments obtained 16 days after onset of symptoms in the upright position deviated ipsilesionally (3.7° on average) whereas in roll-tilted positions roll under-compensation – being clearly increased compared to the healthy controls – was noted. At follow-up, large contralesional SVV deviations in the upright position (averaging -15.2°) were found. Trial-to-trial variability at follow-up remained increased and changed little compared to the initial evaluation.

Patient 5 (UM)

This 59-year-old male patient presented with vertical diplopia worsening when looking to the right, hypersomnia, and attention deficits. With MR-imaging, a sub-acute ischemic lesion within the right paramedian anterior thalamus and within the left paramedian posterior thalamus was found. No mesencephalic involvement could be depicted. We hypothesised that the diplopia was due to a central left-sided fourth nerve palsy caused by a transient compression of the left midbrain resulting from oedema of the left paramedian thalamic infarction. The first assessment of subjective vertical in this patient was delayed (33 days after onset of symptoms) and within the normal range, showing no offsets of SVV in upright position. In this patient, no follow-up SVV measurements were obtained.

Patient 6 (SJ)

This 61-year-old male patient initially presented with hypersomnia and impaired cognition. With MR-imaging, a left-sided thalamic lesion affecting both the central and rostral paramedian thalamus and the posterolateral thalamus (including the nucleus ventro-oralis intermedius [Vim] and the nucleus ventrocaudalis externus [Vce]) was found. There was no evidence for midbrain involvement. SVV measurements (obtained 4 days after the first clinical symptoms) showed contralesional, CW deviations (4.3° on average) in the upright position, whereas at 90° ear down position (both RED and LED) deviations consistent with roll under-compensation were increased compared to the healthy control subjects. Trial-to-trial variability in the upright position was within normal range, however, in roll-tilted positions precision of adjustments was clearly impaired. In this subject, no follow-up SVV recordings could be obtained.

Summary of findings

A total of five out of six patients showed shifts of SVV in the upright position in the sub-acute stage, either in the clockwise ($4.5 \pm 0.9^\circ$; mean ± 1 SD; trials with CW and CCW arrow rotations pooled) or counter-clockwise ($-8.4 \pm 3.3^\circ$) direction. In three out of these five patients, deviations were towards the side of the lesion whereas in the remaining two patients the shifts were contralesional. In the two patients with sub-acute cerebellar lesions (DD and EW) and in the patient with a left mesencephalic lesion (MK) including the MLF and the INC shifts from roll under-compensation towards roll over-compensation in roll-tilted positions were found, whereas two patients (FK and SJ) yielded increases in roll under-compensation. In all these patients, the pattern could be explained by combining an offset of SVV in an upright position with body-position-dependent changes in SVV errors in roll-tilted positions shifting from A-towards E-effects or vice versa (yielding increasing A-effects). One patient with a bilateral paramedian thalamic lesion (UM) showed bilaterally intact CVP both clinically and when testing the SVV. However, in this patient SVV recordings were delayed by more than a month relative to the onset of complaints. An impairment of the CVP in the earlier acute/sub-acute stage therefore cannot be excluded in this patient, however, based on the MR-imaging (showing no signs of posterolateral thalamic or mesencephalic involvement), it would be unexpected. Precision of adjustments was decreased in four out of six patients (EW, MK, FK, and SJ), but the pattern of modulation (i.e., increased trial-to-trial variability with increasing whole-body roll tilt) was preserved.

In the follow-up SVV measurements approximately four months later, verticality perception in upright and roll-tilted positions was either improved ($n = 1$) or had normalised completely ($n = 2$) in terms of accuracy and precision in three out of four patients. One patient with a ponto-mesencephalic dorsal haemorrhage (FK), however, showed worsening of both clinical symptoms and SVV errors at follow-up. Precision of adjustments remained poor. We attributed these findings to a newly developed hypertrophic degeneration of the right inferior olive.

Discussion

The found changes of SVV deviations in the sub-acute stage of patients with lesions along the CVP suggest that body-position-dependent changes of SVV errors, when roll-tilted, occur on top of an SVV error in an upright position. This result is most consistent with hypothesis 2 (see fig. 1). Whereas in patients with cerebellar and mesencephalic lesions deviations were shifted towards roll over-compensation (E-effect), increasing roll under-compensation (A-effect) was noted in one patient with a ponto-mesencephalic (FK) and in one patient with a unilateral posterolateral and paramedian thalamic (SJ) lesion. Such increases or decreases of A-effects and shifts towards E-effects over the entire roll plane are likely to be related to the lesioned CVP and suggest altered central processing of graviceptive input. Considering the often inhibitory function of vestibulo-cerebellar

structures, the observed E-effects in patients with cerebellar lesions could be interpreted as loss of cerebellar inhibition. In the patient with a paramedian mesencephalic lesion (MK), the increased E-effects could be related to impaired processing of inhibitory cerebellar input. In the two patients with increased A-effects, a stronger impact of inhibitory cerebellar input could hypothetically provide an explanation.

We observed both ipsi- and contralesional deviations of the SVV in the upright position. Similarly, the direction of the deviations (ipsilesional vs. contralesional) also varied in the two patients with unilateral cerebellar lesions and likely depended upon the location of the cerebellar lesion. Whereas a contralesional shift was noted when the dentate nucleus was affected (EW), an ipsilesional shift was observed when this structure was spared (DD). Previously, contraversive SVV tilts in patients with acute cerebellar stroke have been related to lesions of dentate nucleus [22] or the cerebellar nodulus [21], whereas in patients with ipsiversive SVV tilts lesions of the biventer lobe, the inferior semilunar lobe, the tonsils and the middle cerebellar peduncle were noted, with the dentate nucleus being spared [22]. These descriptions match our observations well.

Within the brainstem, it was proposed that more caudal (ponto-medullary) lesions yield ipsiversive SVV deviations whereas more cranial (ponto-mesencephalic) lesions result in contraversive SVV tilts [1, 20]. In the current study, ipsilesional SVV shifts were noted in a patient with a mesencephalic lesion including the MLF and the INC in the sub-acute stage (MK), which is opposite to previous observations. Noteworthy, in this subject, SVV deviations shifted over time, being contralesional at follow-up. Possibly the direction of SVV deviations in mesencephalic lesions varies over time and may be ipsilesional in earlier stages. In another patient (FK) with a ponto-mesencephalic haemorrhage, we observed an ipsilesional shift in the sub-acute stage, which would be in agreement with the findings from Brandt and Dieterich.

Whereas posterolateral thalamic lesions presented with deviations of SVV in a majority of cases in a study reported by Dieterich and Brandt, deviations in perceived direction of gravity in patients with anterior paramedian thalamic lesions were linked to additional midbrain tegmental involvement [4]. In the two patients with paramedian thalamic lesions studied here, one (SJ) showed a contralesional shift, which was associated with posterolateral thalamic involvement (including the Vim and Vce) with MR-imaging. Both the Vim and Vce have been reported to process graviceptive signals, yielding ipsi- or contraversive SVV tilts without concomitant OTR [4]. The other patient (UM) initially had signs of a midbrain involvement (vertical diplopia on lateral gaze, possibly associated with a nuclear trochlear nerve palsy), however, when recording the SVV in this patient (with a delay of 33 days after symptom onset) we noted intact perception of verticality along with diminished vertical diplopia. In this subject, it is hypothesised that the thalamic lesion transiently compressed midbrain structures, leading to a nuclear fourth nerve palsy and explaining the vertical diplopia. With MR-imaging this patient presented with no involvement of midbrain structures that belonged to the CVP (such as the MLF and the INC).

The decreased precision of adjustments noted in four patients reflects more uncertainty about self-orientation in space due to impaired central processing of bilateral vestibular input. Improvements of accuracy and precision of verticality perception within four months after lesions along the CVP demonstrate that the body-position-dependent SVV errors observed in the sub-acute stage are readjusted, most likely as a result of central compensation. However, as shown in a patient with a dorsal ponto-mesencephalic haemorrhage and hypertrophic degeneration of the right inferior olive (Mollaret degeneration) at follow-up (see [26] for review), interruption of the rubro-dentato-olivary tract (termed 'Guillain-Mollaret triangle' [27]) can interfere with recovery.

Evaluation of internal estimates of direction of gravity both in terms of accuracy and precision is a sensitive means to quantify the integrity of the CVP. During rehabilitation, patients with lesions along the CVP may first regain their ability to estimate direction of gravity when upright. However, they may still demonstrate difficulties (as reflected in increased A- or E-effects and larger trial-to-trial variability) in the same task when roll-tilted. When assessing the patient's behavioural skills with regards to perceived direction of gravity, restriction to an upright position may underestimate residual symptoms and may therefore lead to premature cessation of rehabilitative efforts. Based on our data, we propose assessing the integrity of the CVP in various roll-tilted positions also.

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