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Postural control during galvanic vestibular stimulation in patients with persistent perceptual–postural dizziness

Josephin Woll[1] · Andreas Sprenger[1,2] · Christoph Helmchen[2]

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Abstract

Over the past years galvanic vestibular stimulation (GVS) has been increasingly applied to stimulate the vestibular system in health and disease, but not in patients with persistent postural–perceptual dizziness (PPPD) yet. We functionally tested motion perception thresholds and postural responses to imperceptible noisy (nGVS) and perceptible bimastoidal GVS intensities in patients with PPPD with normal vestibulo-ocular reflexes. We hypothesized that GVS destabilizes PPPD patients under simple postural conditions stronger compared to healthy controls. They were compared to healthy subjects under several conditions each with the eyes open and closed: baseline with firm platform support, standing on foam and cognitive demand (count backward). Low and high GVS intensities (range 0.8–2.8 mA) were applied according to the individual thresholds and compared with no GVS. PPPD patients showed a reduced perception threshold to GVS compared to healthy control subjects. Median postural sway speed increased with stimulus intensity and on eye closure, but there was no group difference, irrespective of the experimental condition. Romberg's ratio was consistently lower during nGVS than in all other conditions. Group-related dissociable effects were found with the eyes closed in (i) the baseline condition in which high GVS elicited higher postural sway of PPPD patients and (ii) in the foam condition, with better postural stability of PPPD patients during perceptible GVS. Group and condition differences of postural control were neither related to anxiety nor depression scores. GVS may be helpful to identify thresholds of vestibular perception and to modulate vestibulo-spinal reflexes in PPPD, with dissociable effects with respect to perceptible and imperceptible stimuli. The sway increase in the baseline of PPPD may be related to an earlier transition from open- to closed-loop mode of postural control. In contrast, the smaller sway of PPPD in the foam condition under visual deprivation is in line with the known balance improvement under more demanding postural challenges in PPPD. It is associated with a prolonged transition from open- to closed-loop postural feedback control. It could also reflect a shift of intersensory weighting with a smaller dependence on proprioceptive feedback control in PPPD patients under complex tasks. In summary, GVS discloses differences between simple and complex balance tasks in PPPD.

Keywords Persistent perceptual–postural dizziness · Postural control · Galvanic vestibular stimulation

Introduction

The vestibular system not only stabilizes gaze during head movement and locomotion by means of the vestibulo-ocular reflex, but it also substantially contributes to stance and gait control. Postural control of patients with unilateral vestibular failure (UVF) is characterized with acute lateropulsion while patients with bilateral vestibulopathy (BVF) notice oscillopsia during locomotion and unsteadiness of gait and posture. One way to test the vestibulo-spinal control systems is to record postural sway speed during additional vestibular stimulation, e.g., by vestibular-evoked myogenic potentials [1] or galvanic vestibular stimulation (GVS). GVS offers the opportunity to stimulate the vestibular afferents without moving the head [2, 3] and it allows stimulating both sides separately, in contrast to the head impulse test. The stimulus produces stereotyped automatic postural and ocular responses with a strong ear-down roll perception towards the cathodal side [4, 5]. GVS applied to an upright subject induces postural sway towards the side of the anodal

✉ Christoph Helmchen
Christoph.Helmchen@neuro.uni-luebeck.de

[1] Institute of Psychology II, University of Luebeck, Lübeck, Germany

[2] Department of Neurology, University Medical Center Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

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electrode with good test–retest reliability by modulating the firing rate of vestibular nerves [3]. GVS stimulates both otolith and semicircular canal afferents, but may also influence vestibular hair cells [6]. Cathodal GVS increases while anodal polarization reduces discharge rates in vestibular nerve afferents thus differentially modulating activity in the vestibular–spinal nerve bundle thereby altering antigravity muscle tone [2].

Accordingly, GVS has been experimentally used over the last decades not only to study behavioral responses but also brain regions' activity in response to vestibular stimulation, largely using fMRI [7–10].

GVS is capable of eliciting behavioral, cognitive and postural changes in healthy controls and patients. It evokes sensation of body rotation [11] and it affects verticality perception, i.e. GVS deviates the subjective visual vertical towards the anode which shifts to the cathode after GVS [12] and it changes planned trajectories during walking [13]. Stimulation intensity is crucial but currents of 2 mA seems to reliably elicit vestibular perception while stimulus duration seems to have no effect on perception intensity [14].

Even very weak, imperceptible GV stimuli (< 0.5 mA) can elicit behavioral changes in healthy subjects and patients with unilateral vestibulopathy, i.e. latero-lateral postural sway towards the anodal side on eye closure which becomes asymmetric in patients with unilateral vestibulopathy [5]. Imperceptible low-intensity GVS has already been used to enhance the attenuated vestibular signal in patients with bilateral vestibulopathies (BVF). This is thought to be accomplished by stochastic resonance [15] in which a weak (vestibular) non-linear signal can be facilitated by adding some concurring interfering signal, i.e. noise [16], which lowers the system's detection threshold. This signal facilitation operates best with weak subthreshold stimuli [17], about 0.1–0.5 mA [18], whereas a further increase in noise intensity degrades information transfer [19]. Changing the stimulus frequency (0–30 Hz) did not change the effects [20].

Using white noise (noisy GVS, nGVS) BVF patients improved body balance during standing with the eyes closed [21] and dynamic walking, particularly during slow walking [22]. nGVS facilitates vestibulospinal reflexes by lowering detection thresholds [17]. This improves postural stability in young [18] and elderly healthy persons which—when applied with prolonged stimulation duration—continues several hours after stimulus cessation implying neural plasticity in the vestibular system [23]. nGVS also seems to enhance information transfer in the central nervous system; i.e. it improves postural stability, e.g., in patients with Parkinson's disease [24–26].

GVS with higher binaural bipolar peak current levels (3–5 mA) with constant current profile has been used to disrupt postural and gait stability [19]. It induced a similar pattern of postural instability as found in BVF patients suggesting that higher, perceptible current GVS can even be used as a model to examine postural instability of vestibular origin. High current, perceptible GVS has been applied in chronic UVF patients who demonstrated an increase in postural sway under visual and proprioceptive deprivation, compared to healthy subjects [27].

Patients with persistent postural–perceptual dizziness (PPPD) complain about postural and gait imbalance in the absence of quantitative sensory or cerebellar abnormalities [28, 29]. The underlying mechanisms are suspected to involve alterations in functioning of postural control or spatial orientation. PPPD is characterized by chronic perceived dizziness, with symptoms waxing and waning in severity, exacerbated in upright posture and during active or passive motion and exposure to large visual field stimuli, sometimes situation-related worsening of postural unsteadiness, with improvement on cognitive distraction [30] reflecting an exaggerated attentional focus on postural adjustments, in contrast to healthy subjects [31]. PPPD is often precipitated by episodic conditions that caused unsteadiness, which may be vestibular syndromes (e.g., BPPV) or psychological stress. Generally, it is thought to arise from the mismatch between 'bottom-up' (vestibular/proprioceptive sensory) inputs and maladaptive signals from 'top-down' attentional control systems [32].

Previous studies have suspected that patients with phobic postural vertigo (PPV), a related (predecessor) disorder or even a subtype of PPPD [28, 29], have lowered thresholds of detecting multisensory signals stabilizing balance. Moreover, control strategies of postural adjustments are different in PPV patients compared to healthy persons: on posturography, they exert inappropriate postural imbalance during standing under easy balance conditions which paradoxically improves with increasing task difficulty (i.e. tandem stance) or cognitive distraction [33, 34]. Patients use with respect to the task inappropriate postural control strategies, i.e. increased co-contractions of lower limb antigravity muscles, which healthy persons only use in complex balance task (e.g., tandem stance) when they focus attention on balance maintenance [34–36]. Several explanations have been offered which are suspected in PPPD as well: first, patients lower thresholds of sensory detection which leads to earlier initiation of compensatory body sway movements opposite in direction to the perceived body deviation [37, 38]. For example, weighting of intersensory input may be shifted to visual cues which is supported by behavioral (e.g., visual dependence) and imaging evidence [39, 40], a pattern which is also found following vestibular lesions [41–43]. Second, abnormal, e.g., shorter transition from open- to closed-loop postural control might account for this behavior [44] with increased muscle co-contraction [34, 45]. Stabilogram diffusion analysis has been used to quantify postural control behavior by calculating the dynamic mean-squared

displacement of the center of pressure (CoP) in the time interval in which the displacement develops [44]. In healthy subjects, CoP is persistent over short-time intervals but becomes anti-persistent after longer time intervals (> 3 s). This time point (calculated by intersections of curves, see methods and Fig. 5) has been proposed to reflect the transition from open- to closed-loop postural control systems, in which the control changes from a feed-forward (governed by motor commands placing the subjects into the desired position) to a largely feed-backward driven control mode (e.g., sensory signals) [34, 45].

We therefore investigated postural control in PPPD patients during perceptible and imperceptible GVS in different experimental conditions with varying postural complexity and cognitive demand. All conditions were examined with the eyes open and closed due to the strong impact of visual deprivation on postural control in PPPD patients [33]. We hypothesized increased postural imbalance of PPPD patients with perceptible GVS perturbation in easy balance conditions (firm platform) which reduces with larger balance task complexity.

Methods

Participants

Twenty-four right-handed patients with PPPD (age range 24–68 years, mean age 50.23 ± 10.7 years, 69% female), diagnosed according to the PPPD guidelines [28], recently published in a consensus statement of the Barany society (http://www.jvr-web.org/ICVD.html) were enrolled in this study. Mean disease duration was 3.59 ± 4.5 years. The protocol with the letter of information and written informed consent was approved by the local ethics committee of the University of Luebeck (RIB: AZ 17-036). PPPD patients were recruited from the University Centre for Vertigo and Balance Disorders. Written informed consent was obtained from all participants of this study. All patients complained of chronic perceived dizziness (24/24) with considerable reduction of quality of life. Severity was waxing and waning throughout daytime. Dizziness was exacerbated in upright posture (19/24), locomotion (22/24) and exposure to large moving visual field stimuli (15/24). Eight patients had a history of previous vestibular disease [benign paroxysmal vertigo ($n = 5$), history of previous unilateral vestibulopathy ($n = 2$), vestibular migraine ($n = 1$)] which resolved in all of them by > 3 years ago. Ten patients had previous events with psychological distress episodes precipitating chronic dizziness. None of the patients had abnormal vestibular functions on clinical and quantitative recordings (quantitative head impulse test, caloric irrigation, subjective visual vertical) at the time of enrollment. Using conventional dizziness scores, they had a mean of 44.15 ± 23.9 in the dizziness handicap inventory score (DHI) and 37.8 ± 21.8 in the vertigo symptom scale (VSS). The Depression and Anxiety Stress Scale (DASS) (http://www.psy.unsw.edu.au/groups/dass) was used to characterize psychological comorbidity, i.e. depression, anxiety and psychological stress. Age-matched 23 healthy subjects served as controls (age range 23–71 years, mean age 44.3 ± 14.53 years, 56% female). Exclusion criteria included persistent uni- or bilateral vestibulopathy, the use of tranquillizers, consumption of alcohol and the inability to stand without assistance.

Galvanic vestibular stimulation (GVS)

To minimize potential nociceptive stimulation of higher GVS the stimulation site was pre-treated with local anesthetics prior the experiment (Anesderm® lotion, Pierre Fabre Dermo-Kosmetik GmbH, Freiburg/Germany). The current stimulator (DS5 model, Digitimer Ltd., UK) delivered bilateral mastoid galvanic stimulation with skin contact electrodes provided by EasyCap GmbH (Herrsching/Germany). This stimulator has also been used and approved in other centers and studies, e.g., [9, 26]. The skin surface was cleaned again and dried before contact electrodes with commercial contact paste were attached above the mastoid bilaterally.

Individual sensory (vestibular) thresholds were obtained by applying 10 s 1 Hz alternating stimulation, i.e. low-frequency alternating current which passed between the two mastoid electrodes. The ramp stimulus profile hampered sharp transients at stimulus onset and offset (ramp onset and offset of 100 ms duration) with a stimulation plateau of 300 ms leading to perceived head and body tilt (Fig. 5a, e). Threshold testing started with an above threshold current (usually 1 mA). Subsequently, the stimulus intensity was decreased gradually in steps of 0.05 mA until the subject reported no vestibular sensations anymore. Then the procedure started again from a low threshold (0.20 mA) gradually increasing in steps of 0.05 mA until the subject reported vestibular sensations again, i.e. a perception of body motion. The threshold was verified by varying the stimulation intensity until a stable threshold was found. All subjects indicated a medio-lateral motion direction. Previous studies have shown that thresholds obtained using perceptional responses were not different from those obtained by GVS induced quantitatively analyzed body motion [18].

The following four stimulation intensities were used: no current (NoGVS), white noise (nGVS; frequency ranging from 0.02 to 20 Hz, with a maximum of 80% of the current at perception threshold), low (0.5 mA above the perceived threshold) and high intensity current (1.5 mA above the perceived threshold). Each GVS-stimulus was examined twice,

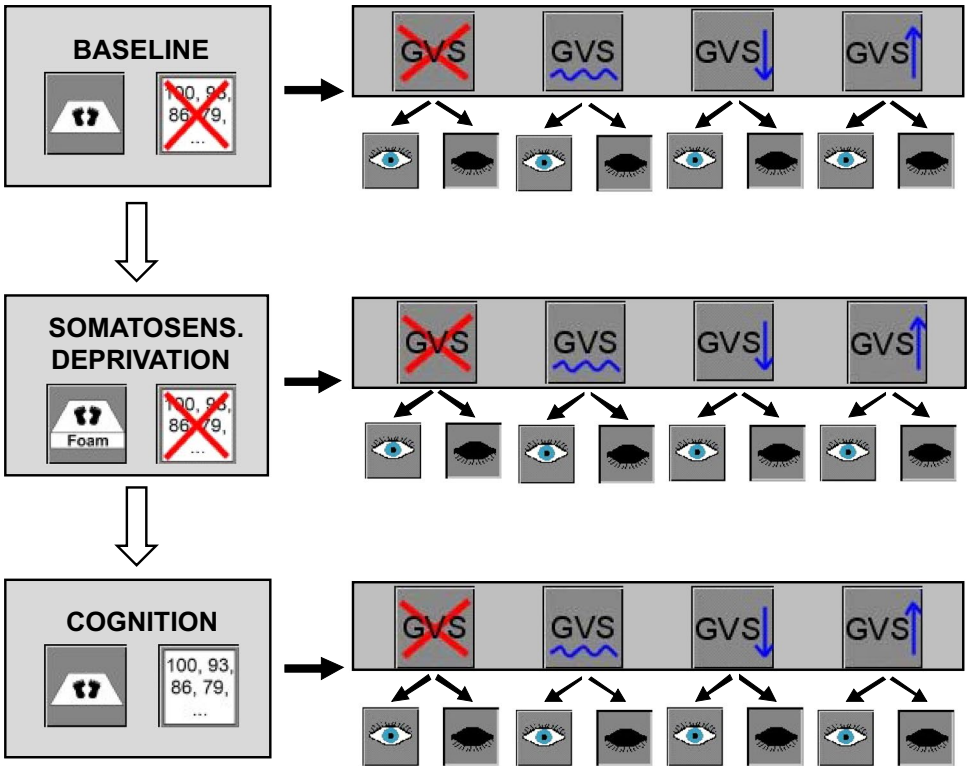


Fig. 1 The experimental setup is illustrated: four stimuli (noGVS, noisy GVS, low and high intensity perceptible GVS) are applied, each one with the eyes open and closed, in three experimental conditions: baseline with firm platform support, foam (somato-sensory deprivation) and counting backwards (cognition) while standing on the firm platform

with the eyes open during fixation a gaze straight ahead target and with the eyes closed in each experimental condition (Fig. 1) resulting in 24 recording sessions (20 s each). Sequence of experimental conditions was randomized.

Electrophysiological and psychophysical recordings of vestibular function

All standardized vestibular tests showed data within normal limits without group differences. Vestibular function of participants was examined by video-oculography with caloric irrigation [bithermal cold (27°) and warm (44°) caloric irrigation] and quantitative head impulse testing (qHIT). Eye and head movements were recorded by the EyeSeeCam® HIT System (Autronics, Hamburg, Germany) at a sampling rate of 220 Hz; VOR gain was determined by robust linear regression of eye and head velocity starting at head velocity > 10°/s to 95% of peak head velocity using Matlab®. Quantitative HIT was delivered by passive head impulses (HIT) with rapid small amplitude (10°–15°) horizontal head rotations (3000°/s^2–4500°/s^2) while the participant was sitting on a chair fixating a red LED at a distance of 100 cm. For further details, see [46–49]. Psychophysical perception of the visual vertical was assessed with the head fixed on a chin rest by the subject's adjustment of a bar to the perceived visual vertical without any spatial orientation clues in a dotted half-spherical dome, which is stationary or dynamic (moving visual background) around the line of sight [50]. The normal range of SVV was defined as deviation of < 2.5°.

Experimental conditions

Posturography was recorded in the upright standing position with the hands hanging next to the trunk for 20 s. At baseline, subjects were asked to stand on the platform with feet (shoes) parallel to each other. We tested the following experimental conditions (Fig. 1) which differed in terms of (i) visual (eyes open/closed; EO/EC), (ii) proprioceptive (foam) input, and (iii) cognitive influences on postural control (dual task with backward counting); for details see [51, 52]. Participants were asked to fixate a target 60 cm in front of the participants' forehead. We used a slab of foam rubber (50 width, 60 cm length, height 10 cm, compression hardness: 3.3 kPa, volumetric weight: 40 kg/m^3) for testing balance control under attenuated proprioceptive feedback.

Posturography

We used a Kistler force platform (Model 9260AA6, Kistler Instrumente AG, Winterthur, Switzerland; 50 cm width,

60 cm length) equipped with piezo-electric 3-component force sensors for recording postural changes during the above-mentioned experimental conditions in a similar way as described elsewhere [53–55]. Postural sway signals were bidirectionally filtered (50 Hz Gaussian filter) to eliminate low-amplitude recording noise [56]. The platform recorded torques and sheer forces with six degrees of freedom using force transducers with an accuracy better than 0.5 N. The displacement of the center of pressure (CoP) in the medial–lateral (ML) and the anterior–posterior (AP) directions were recorded and the sum vector calculated using Matlab® (R2017b, The Mathworks, Natick/MA). Results are given as the median postural sway speed (PSS, in cm/s), calculated from the anterior–posterior (AP) and medio-lateral (ML) movements:

$$\mathrm{PSS} = \mathrm{median}\left(\sqrt{(\mathrm{AP}_i - \mathrm{AP}_{i-1})^2 + (\mathrm{ML}_i - \mathrm{ML}_{i-1})^2} \times \text{sampling rate}\right).$$

Postural sway was recorded in intervals of 20 s duration for off-line analysis (sampling frequency 250 Hz) [52, 57]. PSS has been shown as a robust, discriminative and reliable factor of recording postural balance [58, 59].

Stabilogram diffusion analyses

Stabilogram diffusion analyses (SDA) were performed for the time series of center of pressure displacements (CoP) in the mediolateral (ML), anterior-posterior (AP) and planar direction [44, 45, 60] by computing

$$\langle \Delta x^2 \rangle = \langle [x(t + \Delta t) - x(t)]^2 \rangle.$$

Mean-squared distances of a point $x(t)$ to a point $x(\Delta t)$ were calculated for each x and for increasing Δt from 0 to 10 s (‹o› denotes the mean of the time series). Mean-squared displacements (MSD) were plotted against Δt time intervals for each subject (Fig. 5c, g). In order to determine the transition point from short-term to long-term diffusion (i.e. open- and closed-loop postural control), the following procedure was performed: linear regressions (robustfit within Matlab®) were performed on MSD for the time intervals of 0.1–2.0 s. From these regressions, the root mean square (RMS) of each regression's residuals was obtained. A significant increase of RMS was regarded as the time limit for the optimal regression of short-term diffusion. The threshold for a significant increase was the fourfold standard deviation of RMS values of the time intervals from 0 to 0.5 s. Plots of all subjects and all conditions verified optimal regression for short-term MSD. The transition point from short-term to long-term diffusion was defined by the crossing point of linear regression of the short-term MSD and linear regressions from the MSD of time intervals from 1 to 4 s [44, 45, 60].

Statistical analysis

Power calculation prior to the study predicted a necessary group size of at least 23 subjects per group [61]. Statistical analyses were performed with SPSS (22.0.0.2; IBM Corp., Somers NY). Analyzing the postural sway speed, the factors TARGET VISIBILITY (eyes open/closed), CONDITION [baseline, proprioception (foam), cognition (count back task)] and STIMULATION (noGVS, nGVS, lowGVS, highGVS) were taken as within-subject factors and GROUP as between-subjects factor. The effects of visual deprivation on postural stability were determined by Romberg's ratio computing PSS with the eyes closed/eyes open [62]. Hence analyzing Romberg's ratio the factor TARGET VISIBILITY was eliminated, therefore all other factors were included in the ANOVA. In some comparisons sphericity requirement was violated. Therefore, we report F values with Greenhouse–Geisser correction but report degrees of freedom (df) uncorrected in order to show the factorial analysis design. Statistical comparisons were performed parametric unless stated otherwise.

Multi-factorial ANOVA with the above-mentioned factors was performed. Significance levels of post hoc tests were Bonferroni corrected for multiple testing. Statistical differences were regarded as significant for values $p < 0.05$. Error bars indicate mean values (M) and standard error of mean (SE). Correlation analyses were performed using Spearman-Rho coefficient unless otherwise stated.

Results

Psychophysics

The perception threshold of GVS was significant lower in PPPD patients (0.31 ± 0.2 mA) compared to controls (0.47 ± 0.19 mA) ($t(47) = -3.069$ ($p = 0.004$; Fig. 2a). Participants reported no pain during GVS. The threshold was not correlated with the level of anxiety ($r = 0.112$; $p = 0.56$). Figure 2b shows mean values ($\pm$SEM) for depression, anxiety and stress in patients and healthy controls which significantly differed between groups.

Postural data

Generally, postural sway speed differed between conditions ($F(2,74) = 52.34$, $p = 0.001$) but not groups. Post hoc tests revealed significantly stronger sway in the FOAM condition compared to the other conditions: Baseline-Foam ($p < 0.001$) and Cognition-Foam ($p < 0.001$), irrespective of GVS intensity or target visibility (eyes open vs. closed). Data revealed a significant interaction of CONDITION

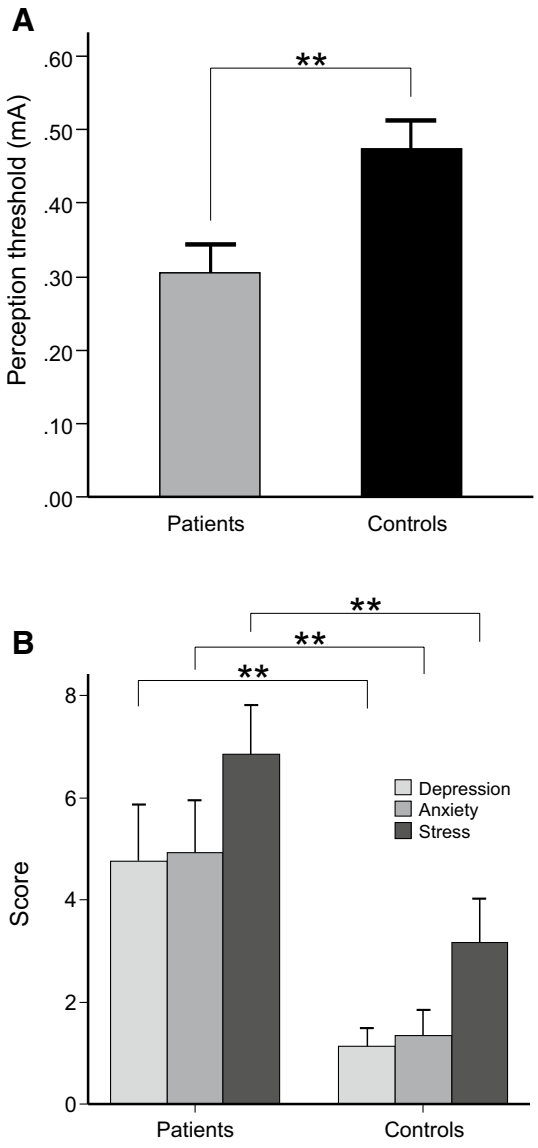


Fig. 2 **a** Perception thresholds to GVS are shown for PPPD patients and healthy participants (upper panel). Patients had a significantly lower threshold ($t(47) = -3.069$; $p = 0.004$). Error bars indicate standard error of mean. **b** Mean values (± SEM) for each of the components of the Depression Anxiety Stress Scale are displayed for PPPD patients and healthy control subjects (**$p < 0.005$)

× GROUP ($F(2,74) = 4.78$, $p = 0.05$). There was a trend towards higher PSS of PPPD patients in the Foam condition ($p = 0.078$). Generally, Romberg's ratio did not differ between groups ($F(1,37) = 0.76$, $p = 0.388$) (PPPD 1.66 ± 0.12; Control 1.5 ± 0.13). There was a significant main effect for VISUAL INPUT (i.e. eyes open vs. closed, EOEC) ($F(1,37) = 117.14$, $p = 0.001$) with increased PSS on eye closure but without group differences [interaction EOEC × GROUP; $F(1,37) = 3.06$; $p = 0.89$].

PSS differed significantly between GVS intensities (main effect of STIMULATION, $F(3,111) = 67.70$; $p < 0.001$), i.e. it increased with stimulus intensity (Fig. 3). Except for the comparison nGVS vs. no GVS all other comparisons were significant different in the post hoc analysis ($p < 0.001$). Within each group, PSS with high GVS was significantly higher than with the other GVS intensities (main effect for GVS; $p < 0.001$). The PSS increase with GVS was different between the conditions [interaction GVS × CONDITION ($F(6,222) = 24.2$; $p < 0.001$)], i.e. with stronger increase in the foam compared to both other conditions, but not different between the groups [interaction of GVS × GROUP was not significant; ($F(3,111) = 1.93$; $p = 0.158$)]. However, groups differed with respect to GVS response and condition [significant interaction of GVS × GROUP × CONDITION; ($F(6,222) = 6.20$; $p < 0.001$)].

During GVS, visual input had a crucial effect on PSS and differed between groups (Fig. 3): PSS increased on eye closure and GVS intensity [interaction GVS × visual ($F(3,111) = 43.24$; $p < 0.001$); GVS × visual × group ($F(3,111) = 4.27$; $p < 0.05$)]. In PPPD, PSS decreased with nGVS compared to all other stimulations which just failed significance in the control group.

Romberg's ratio significantly differed between GVS intensities ($F(3,35) = 18.44$, $p < 0.001$) and the conditions ($F(2,36) = 53.74$, $p < 0.001$), and there was an interaction of CONDITION × GROUP ($F(2,36) = 14.23$, $p < 0.001$), of GVS × CONDITION ($F(6,32) = 3.53$, $p = 0.018$) and a triple interaction of GVS × CONDITION × GROUP ($F(6,32) = 6.77$, $p < 0.001$).

Post hoc analysis of the separate conditions revealed the following: in the baseline condition, PSS was significantly higher in PPPD patients (Fig. 3; $p = 0.013$) but there were no differences between nGVS and noGVS, irrespective of target visibility (EO/EC).

Romberg's ratio was different between GVS ($F(3,111) = 5.29$; $p = 0.007$), i.e. it was significantly lower during nGVS compared to the other GVS conditions ($p < 0.001$; Fig. 4) but not between the groups [interaction GVS × GROUP: $F(3,111) = 0.63$; $p = 0.538$].

In the foam condition, PSS was significantly lower with nGVS compared to noGVS ($p = 0.004$; for both groups (PPPD: M_noGVS-M_nGVS; $p = 0.002$), low ($p = 0.032$) and high GVS ($p = 0.001$). However, GVS effects also differed between groups [($F(1,46) = 9.46$; $p = 0.004$); interaction GVS × GROUP $F(3,138) = 5.44$; $p = 0.005$)].

Interestingly, PPPD patients showed lower PSS during both perceptible GVS. This effect was only significant on eye closure (lowGVS: $p = 0.007$ and highGVS: $p = 0.005$, Fig. 3). With visual fixation, PSS increased significantly only with highGVS compared to the other stimulations. There was no difference between nGVS and noGVS. Romberg's ratio increased with GVS intensity ($F(3,138) = 13.42$; $p < 0.001$) but it was significantly reduced during nGVS (M_noGVS-M_nGVS, $p = 0.001$),

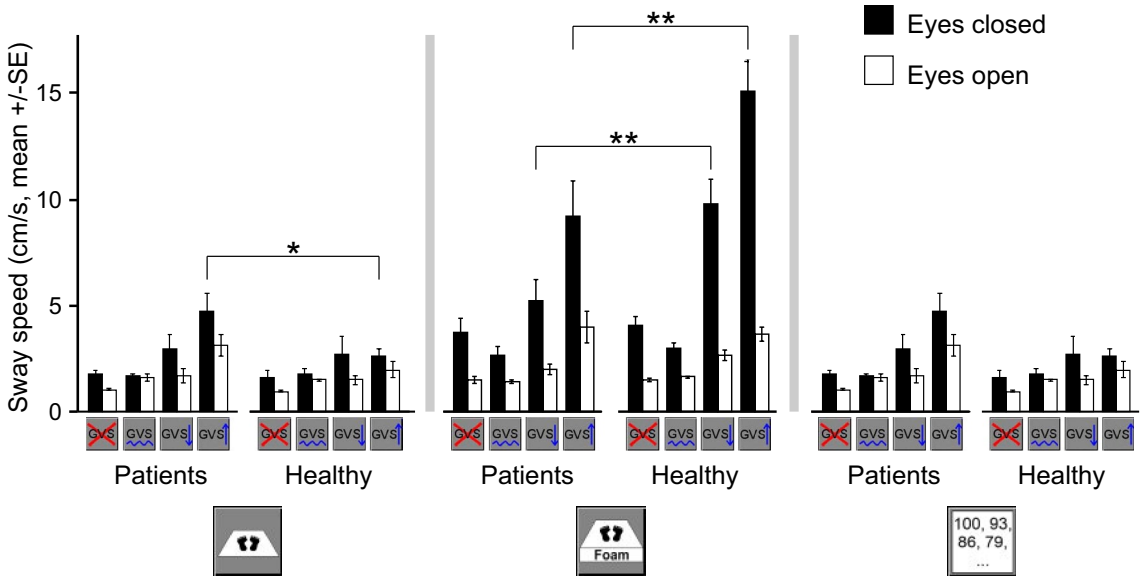


Fig. 3 Postural sway speed (in cm/s) is displayed for patients and healthy controls, each group for the four GVS stimuli (noGVS, noisy GVS, low- and high-intensity perceptible GVS), in the three experimental conditions schematically indicated at the bottom. Eyes open (open bar) and eyes closed (black bar) conditions are compared. Significant differences between groups are indicated (±SEM; $*p<0.05$; $**p<0.005$). Sway differences between eyes open and closed were found in almost all comparisons and therefore not shown, for clarity (main effect, see results). Error bars indicate standard error of mean

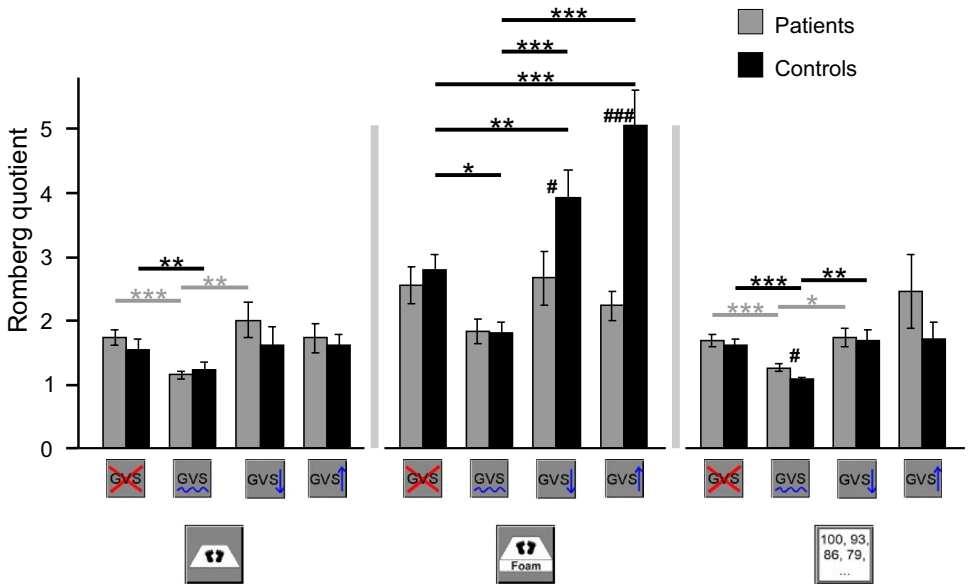
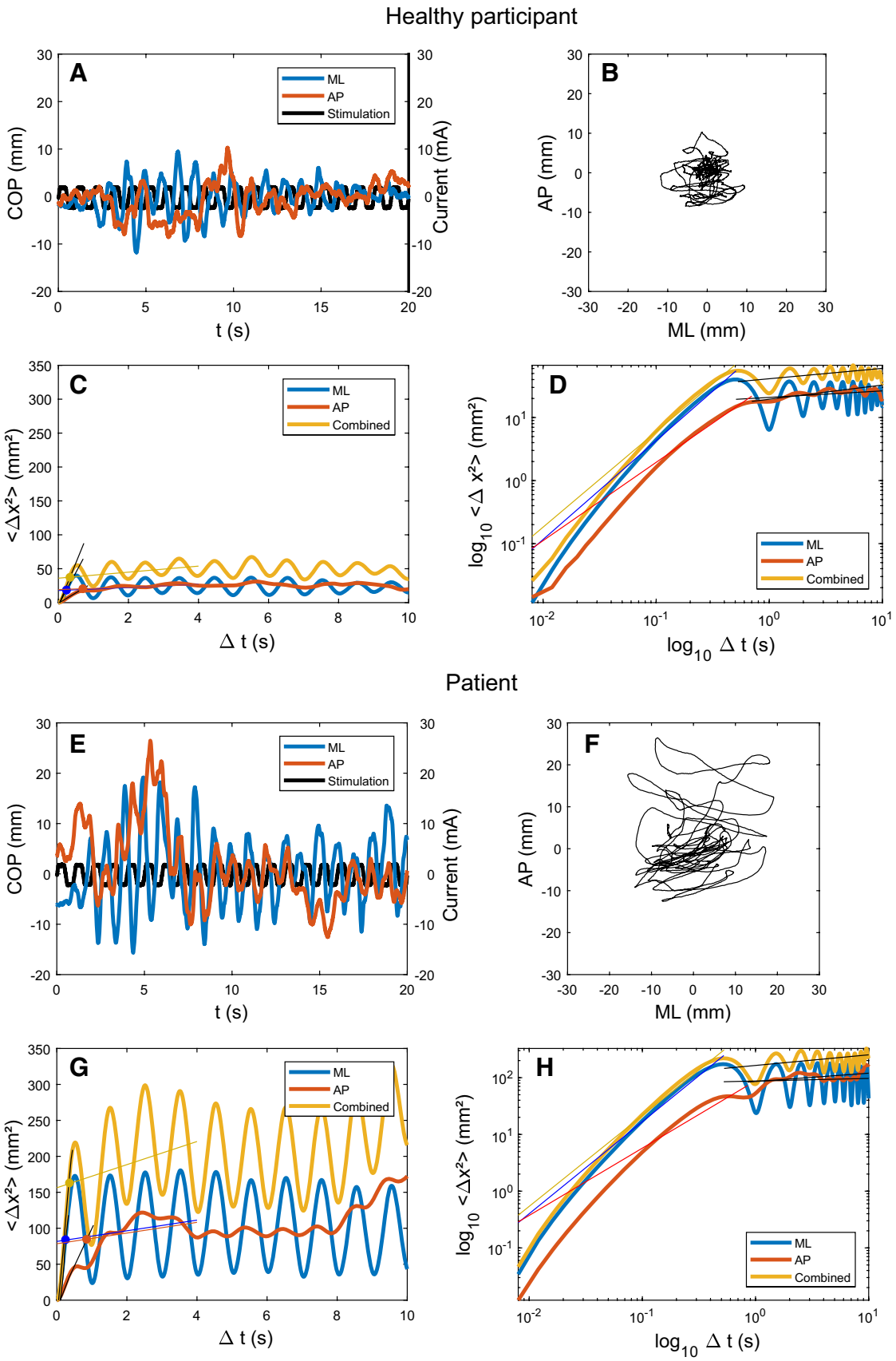


Fig. 4 Postural sway for Romberg's ratio is displayed for patients (grey bar) and healthy controls (black bar), each for the four GVS stimuli (noGVS, noisy GVS, low and high intensity perceptible GVS), in the three experimental conditions schematically indicated at the bottom. Significant sway differences between GVS intensities ($*p<0.05$; $**p<0.01$, $***p<0.001$) and groups are shown ($^{\#}p<0.05$; $^{\#\#\#}p<0.001$). Error bars indicate standard error of mean

particularly in the FD patients (PPPD: M_noGVS-M_nGVS, $p=0.05$); but also in the controls (noGVS-nGVS: $p<0.045$; lowGVS-nGVS: $p<0.001$, highGVS-nGVS: $p<0.001$).

Using the motion perception threshold as a covariate there was no main effect for the motion perception threshold ($F(1,45)=3.252$, $p=0.078$), but the group differences in Romberg's ratio persisted ($F(1,45)=4.498$, $p=0.039$) as well as the interaction of GVS × GROUP ($F(3,135)=3.075$, $p=0.049$).

In the cognition condition, similar to the baseline condition, PSS significantly differed between the GVS intensities; i.e. it increased with GVS intensity ($p=0.001$–0.029). PSS during nGVS did not differ from noGVS. There were no group differences [GROUP: ($F(1,46)=1.65$; $p=0.205$); interaction GVS × GROUP ($F(3,138)=0.64$; $p<0.462$)].


Healthy participant
A
ML
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Stimulation
COP (mm)
Current (mA)
t (s)
B
AP (mm)
ML (mm)
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AP
Combined
<Δx²> (mm²)
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D
log10 <Δ x²> (mm²)
log10 Δ t (s)
Patient
E
ML
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log10 <Δx²> (mm²)
log10 Δ t (s)

◂**Fig. 5** Original center of pressure displacement (CoP in mm) recordings are shown for a healthy control (**a, b**) and a patient (**e, f**) during highGVS stimulation with the eyes closed on the solid platform, i.e. one of the experimental conditions with a group-related significant difference (larger sway in PPPD patients). **a, e** shows the CoP over time (s); with mediolateral (ML) and anterior–posterior (AP) displacements. Time course of the galvanic (ramp) stimulus is displaced in black (ordinate on the right; both participants received the same stimulus intensity (2.0 mA) here as both had the same perception threshold of about 0.5 mA). In **b, f** ML and AP trajectories are shown in conventional positional data plots. The mean distance (mm) of ML, AP and the combination (sum) of both traces are displayed over time. The crossing point (CP) is defined by the regression lines of short-term and long-term mean Δx^2 against Δt for a healthy participant (**c**) and a PPPD patient (**g**). **d, h** Log–log plots of data shown in **c, g** allowing a magnified view on the calculation of the crossing point CP with its Δt

On eye closure, the increase of PSS seen in the baseline condition with nGVS compared to noGVS, was not significant any more. However, there was a significant reduction of Romberg's ratio with nGVS compared to noGVS ($p < 0.001$) and lowGVS ($p = 0.016$; Fig. 4).

Since patients had higher anxiety and depression scores (Fig. 2b), we related them to the postural sway in the different conditions to investigate their potential role in the group differences found.

Using the anxiety score as a covariate there was no main effect for anxiety ($F(1,34) = 0.946$, $p = 0.338$) in PSS and in Romberg's ratio ($F(1,34) = 0.451$, $p = 0.506$). Furthermore, there were no interactions of any factor combinations with the anxiety score. All other main effects and interactions remained significant. Multiple correlations between the anxiety score and PSS revealed no significant correlation except for the conditions 'cognition without GVS and with the eyes open' ($r = -0.397$, $p = 0.044$) and 'baseline with nGVS and eyes closed' ($r = -0.438$, $p = 0.041$). Noticeably, in the latter conditions we did not find significant group differences (Fig. 3). There was no correlation for Romberg's ratio with any posturographic value (p always > 0.26). No correlation survived the level of significance when it was corrected for multiple comparisons using Bonferroni's method (p always > 0.35).

Using the depression score as a covariate there was also no main effect for depression ($F(1,34) = 0.379$, $p = 0.542$) in PSS and in Romberg's ratio ($F(1,34) = 0.320$, $p = 0.575$). Furthermore, there were no interactions of any factor combinations with the depression score. All other main effects and interactions remained significant. Although patients had higher depression scores (Fig. 2b), only five patients had depression scores above normal levels: mild (score 10–13; $n = 2$) or moderate (score 14–20; $n = 3$) depression scores. Multiple correlations between the depression score and PSS revealed no significant correlation except for three conditions [baseline with eyes closed during nGVS ($r = -0.495$, $p = 0.019$); foam condition with the eyes open during nGVS ($r = -0.480$, $p = 0.020$); cognitive condition with the closed eyes during nGVS ($r = -0.446$, $p = 0.029$)]. Note that we did not find group differences in the latter conditions (Fig. 3). No correlation survived correction for multiple comparisons (p always > 0.43). There was a correlation for Romberg's ratio with the depression score for baseline condition with lowGVS ($r = 0.630$, $p = 0.003$) but no other condition (p always > 0.07).

In summary, all subjects showed an increase in PSS with perceptible PSS, but patients had smaller increases than healthy subjects in the most demanding condition (eye closure on foam). In all participants, PSS decreased with nGVS compared to all other stimulations.

In addition, we performed linear stabilogram diffusion analysis (SDA) with diffusion plots to examine the characteristics and modes of interaction of open- and closed-loop modes of postural control in PPPD patients [44, 45, 60]. The diffusion plots show the mean-squared displacements of postural sway over the given time intervals (Fig. 5). The point CP, where the linearly fitted regression lines cross, reflects the transition from open- to closed-loop postural control. The time interval to CP (latency) was significantly different between GROUPS ($F(1,49) = 8.57$, $p = 0.005$), main effects were also found for STIMULATION ($F(3,47) = 37.4$, $p < 0.001$) and VISUAL INPUT (eyes open/closed) ($F(1,49) = 9.747$, $p = 0.003$) with shorter latencies with (i) increasing stimulation intensity and (ii) with visual input (Fig. 6a, b). There was a significant group-related interaction of STIMULATION × GROUP ($F(3,47) = 4.315$, $p = 0.008$). Post hoc analysis revealed shorter latencies on eye closure in the baseline condition during highGVS of PPPD patients (PPPD: 0.77 s ± 0.092 and controls 1.06 ± 0.101, $p = 0.044$). Figure 5 shows representative examples of original CoP displacement recordings for a healthy control (Fig. 5a, b) and a patient (Fig. 5e, f) during highGVS stimulation with the eyes closed on a firm platform, i.e. one of the experimental conditions with a significantly larger postural sway speed of PPPD patients (Fig. 3). This increase in patients becomes evident in all comparisons, not only in the positional plots, but also in the linear diffusion stabilograms reflecting CoP displacements over time (Fig. 5a–d vs. e–h).

In the conditions with group-related differences in the postural sway speed (Fig. 3) post hoc tests of latencies to CP during perceptible (low, high) GVS revealed opposite group-related effects in the baseline and foam condition: mean latencies (± SEM) were significantly shorter in patients in the BASELINE condition (firm platform) on eye closure (Fig. 6c, $p = 0.044$), i.e., in a condition with larger PSS of PPPD patients compared to healthy controls. In contrast, patients showed longer latency to CP in the FOAM condition during low but not high GVS (Fig. 6c).

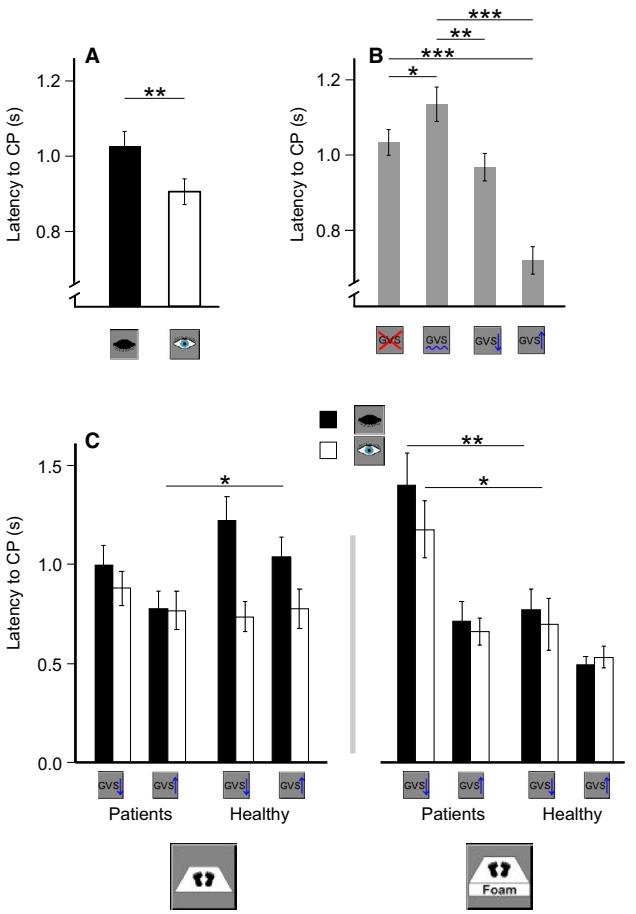

Fig. 6 Mean latencies (±SEM) of the crossing points (transition from open- to closed-loop postural control) are shown with main effects for VISUAL INPUT (**a**), i.e. eyes open vs. eyes closed, and STIMULATION (**b**), i.e. lowGVS, highGVS compared to noisyGVS and no GVS. **c** Mean latencies are shown for the conditions with group-related differences of postural sway in the baseline and foam condition (Fig. 3). Patients have a shorter open-loop phase (shorter latency) on eye closure on the firm platform where they had larger sway speed compared to healthy controls. In contrast, latencies of PPPD patients were longer in the foam condition during lowGVS in which they had less postural sway compared to controls (*$p<0.05$; **$p<0.01$; ***$p<0.001$)

Discussion

While GVS with stimulus intensities above the perception threshold destabilized postural control in our healthy subjects in a GVS intensity-related manner, imperceptible GVS (< 0.5 mA) improved postural stability, particularly Romberg's ratio of PSS. This is in accord with previous studies showing postural instability during perceptible GVS in healthy subjects in a manner similar to baseline recordings of patients with bilateral vestibulopathy [19] or astronauts after the space flight [63]. Likewise, several previous studies showed improvement of postural stability by imperceptible GVS (< 0.5 mA, nGVS) not only of patients with BVF [21], but also of healthy subjects [18].

For the first time, we applied nGVS and perceptible GVS with different intensities in patients with persistent postural–perceptual dizziness (PPPD) [28], according to the Classification of Vestibular Disorders of the Bárány Society (see Patient demographics).

One major finding was the abnormal low GVS-evoked perception threshold for body motion of PPPD patients. This is in line with a proposed lowering of sensory feedback control in PPPD patients, at least in PPV [45], and may reflect the concept of exaggerated attention on vestibular processing [34] or a stronger (fear-related) expectation of anticipated vestibular stimuli. A reduced perception threshold might lead to subjective postural unsteadiness which in turn could facilitate inappropriate postural motor responses to sensory feedback and inappropriate adjustments [64]. A shift of the postural strategy to a more attentional control [65] should have elicited larger postural sway under baseline conditions (in the absence of GVS) which was not the case in our PPPD patients, neither with nor without visual control. This contradicts some data showing increased postural sway in baseline recordings of PPPD patients without GVS, irrespective of visual control [33, 65, 66]. Increased postural instability in our PPPD patients was only found in the baseline condition with perceptible high GVS. Increase in postural sway on eye closure under simple balance tasks has been proposed to indicate that PPPD patients rely more on visual information to assure postural control [35]. However, increased postural sway in our PPPD patients was seen during high GVS in the baseline condition only but not without vestibular stimulation. Perceptible GVS seems to be a method to demask abnormal postural instability on eye closure of PPPD. This is in line with posturography data showing increased sway in PPV patients with additional sensory (vibratory proprioceptive) stimulation [67].

Alternatively, anxiety might have influenced vestibulospinal postural control in PPPD patients [68]. Anxiety has been demonstrated to be a main covariate determining abnormal functional connectivity in PPPD [39, 40]. However, this is unlikely to explain our group differences for at least two reasons: (i) postural responses in the baseline condition did not differ between low perceptible and noGVS stimulation in our PPPD patients and (ii) the provoked postural instability by an additional sensory perturbation was reversed with increasing postural task complexity in our PPPD patients (see foam conditions) which is in accord with previous studies on PPPD patients without additional sensory stimulation [33, 65]. Finally and most importantly, group-related differences were still found when anxiety and depression scores were calculated as covariate (no main effect, no correlation).

The increased sway in simple balance tasks has been related to an inappropriate postural control strategy, i.e. increased co-contractions of lower limb antigravity muscles, which healthy persons only use in complex balance task when they focus attention on balance maintenance [34]. This could indicate that the visual input serves to decrease the stiffness of the lower limbs [44, 64]. Alternatively, a change in the transition of so-called open- to closed-loop postural control [44] may account for the instability of PPPD patients in the baseline condition with high GVS. According to this conceptual framework open-loop control reflects feed-forward mechanism derived from motor commands placing the body in the desired posture in short-term intervals. Closed-loop postural control systems, in turn, rely on multisensory feedback mechanisms that correct drifts from the desired posture. This concept has provided several details about the functional organization of the postural control system [44]. Although the stabilogram diffusion analyses are confounded by the external vestibular stimulus (GVS), our data support the notion that the transition from open- to closed-loop postural control mode is altered in PPPD [45]. We provide some evidence that the short-term open-loop mechanism is shortened in the baseline condition in PPPD, with an earlier transition to closed-loop (sensory feedback guided) control mechanisms which is in line with previous studies on PPPD, without GVS [34, 45, 65]. Our stabilogram diffusion plots showed a shorter open-loop interval in the baseline condition of our PPPD patients (highGVS on eye closure) compared to healthy controls indicating an abnormal open-loop postural control in the condition, in which they showed abnormal (higher) postural sway speed. Feed-forward, open-loop postural control is governed by the cognitive (i.e. fear) modulation of motor commands but not the sensory feedback which determines the long-term, closed-loop postural control [64]. In contrast to previous reports [65], abnormal open-loop control in our PPPD patients was only found on eye closure with GVS but not without vestibular stimulation. Thus, an earlier shift to closed-loop postural control in this condition could therefore reflect stronger sensory feedback reliance on vestibular signal processing. Moreover, latencies to the transition point were longer in the foam conditions of PPPD patients in which they had less postural sway compared to controls. Thus, GVS application may extend the knowledge on the postural control mechanisms on PPPD patients.

The GVS-related increase of postural instability is related to vestibulo-spinal stimulation of functionally normal vestibular afferents both in healthy subjects [2, 19] and our PPPD patients. In contrast, increase in postural instability of BVF patients during perceptible GVS is related to stimulation of abnormal vestibular afferents [69, 70]. In both our groups, postural sway increased with perceptible GVS intensities in a stimulus-dependent manner that did not differ between the groups, despite the reduced differences in perception threshold. This was not only valid for normal stance with visual control, but also on eye closure. A similar increase of body sway with larger GVS has also been found in the deflection of motion walking path [71]. One striking finding in the condition with complex balance demands (with proprioceptive and visual deprivation) was that perceptible GVS destabilized healthy subjects more than PPPD patients. When compared with the baseline condition, it seems that the additional attenuation of proprioceptive signals for postural control destabilize healthy controls more than PPPD patients. This was particularly true when Romberg's ratio is compared (Fig. 4). It was significantly lower in PPPD patients on foam compared to the healthy subjects, but only with perceptible GVS. This could be related to an altered reliance on proprioceptive and possibly also vestibular feedback mechanism in PPPD patients, or an altered shift from open- to closed-loop postural control [64] or a central reweighting mechanism of multisensory processing [29, 38, 40, 42]. For example, reweighting the processing of vestibular, visual and somatosensory information in favor of visual inputs is a suspected mechanism to explain the visual dependence in PPPD that makes patients more susceptible to visually induced dizziness [28, 42]. As the group-related difference in our study was not seen without GVS, only the additional vestibulo-spinal stimulation (low and high GVS) demasked this improvement.

GVS with perceptible stimulus intensities might therefore help to disclose the characteristic postural adjustments of PPPD patients under complex balance tasks which dissociates them from patients with unilateral or bilateral vestibulopathy. GVS should be considered in particular, when visual and proprioceptive signal attenuation alone (without GVS) does not help to identify improvement under higher postural demand.

Several studies have shown the modulation of postural control by imperceptible noisy GVS, in healthy subjects [23, 72], BVF patients [21, 73, 74] and central neurological diseases, e.g., Parkinson's disease [26, 75]. It also improves gait parameters in BVF, particularly during slow walking velocities [76]. The principle of stochastic resonance may not only enhance peripheral signal transfer, but it may also improve signal discrimination in the central nervous system [18]. Postural sway in our PPPD patients with nGVS did not differ from noGVS, but it was significantly lower than during perceptible GV stimuli. Moreover, there was no group difference indicating that both groups used signal improvement by stochastic resonance in a similar way.

On a first glimpse, the missing nGVS effect on postural control could be due to the reduced perception threshold in PPPD patients making nGVS a perceptible stimulus. This is unlikely since all stimuli were adapted to the individual perception threshold. Other studies reporting healthy non-responders to nGVS found no differences in perceived

thresholds between responder and non-responders [18]. This was suggested to be related to an inherently reduction of weighting vestibular signal processing with concomitantly stronger re-weighting of visual and proprioceptive signal integration for postural control [18]. Sensory reweighting by downregulating vestibular signals is a known mechanism of compensation [77–79] which has been assumed to explain balance improvement with supra-threshold GVS [18] and the central adaptation, e.g., in preflight space training by GVS [80].

The leading symptom in patients with functional disorders is the abnormal individual perception of one's own sensory processing. Therefore, rather than comparing the same physical GVS intensities between the groups we matched similar perceptions between the groups by adapting the GVS intensities to the individual perception threshold. Using perceptional matching we found group differences in the foam condition with perceptible GVS that indicated a postural pattern possibly characteristic for PPPD. In future studies, the decreased perception threshold has to be taken into account when PPPD patients are stimulated with normally imperceptible GVS intensities and nGVS since low GV stimuli might elicit postural imbalance which is usually only seen with higher GVS inn healthy controls. In case of comparing GVS-related neural or behavioral responses, we propose to compare equal perceptions rather than physical stimulus intensities.

This could, however, also be taken as a potential limitation of the study. One could argue that different physical stimulus intensities accounted for the behavioral differences on posturography. This is, however, unlikely since PPPD patients showed increased postural sway in the baseline GVS-condition with stimulation intensities being lower than in healthy control participants (due to their reduced motion perception threshold). Moreover, we used the threshold of perceived motion as a covariate in our analysis and the group differences in Romberg's ratio during high GVS persisted. Another potential limitation of this and many other studies on PPPD is the fact that patients were not systematically tested for all vestibulo-spinal reflexes mediated by otolith stimulation (vestibular-evoked myogenic potentials). Therefore, even with normal SVV, we cannot completely rule out an otolith dysfunction for the increased postural imbalance of PPPD patients with highGVS. However, in that case PSS should be larger on foam than in healthy participants, which was not the case.

In conclusion, our study implicates the benefit of using perceptible GVS in examining the postural control of PPPD patients as it discloses differences between simple and complex balance tasks that indicate a better postural control under more demanding conditions, a feature indicative for PPPD, which is, however, not always found without GVS. Future studies will have to examine whether the outlined features of PPPD-associated postural behavior can also be found in other patient groups with dizziness or anxiety disorders to elucidate its specificity.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study has been approved by the University Ethics Committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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