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Activity-dependent modulation of human balance and gaze control

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1. Introduction

The human bipedal upright stance and locomotion relies upon a set of highly flexible and adaptable postural control mechanisms to maintain equilibrium. The postural and locomotor control system is organized in a complex hierarchical network of supraspinal and spinal locomotor regions, which integrate sensory information from the different sensory modalities to initiate corrective or compensatory adjustments of the basic locomotor pattern in order to match changes in the environmental conditions.

Sensory information is provided by the visual, vestibular, and somatosensory system and processed in conjunction with efference copies of the spinal locomotor command. In the central nervous system, the inflow of sensory information from multiple sources is rapidly and selectively processed to distinguish between externally generated sensory information (i.e., exafferent sensory information) and self-generated sensory information (i.e., reafferent sensory information) to consequently produce an activity-specific motor output.

Visual, vestibular and proprioceptive reflexes have traditionally been viewed as the main source of sensory contribution to gaze and balance stabilization during human locomotion. However there is increasing evidence that sensory contributions to balance and gaze control become modulated in dependence of the executed motor activity (Rossignol, Dubuc et al. 2006).

A possible underlying mechanism for this phenomenon was observed in an aquatic animal model in which intrinsic efference copy signals have shown to selectively suppress sensory feedback during tadpole swimming (Lambert, Combes et al. 2012). Accordingly, locomotor efference copy signals originating from spinal neuronal networks (i.e., central pattern generators) are directly conveyed to their respective supraspinal targets to supplement or even replace movement-encoding sensory information.

Such an internal feedforward regulation of posture and gaze can, however, only be efficient if the body and head movements, occurring during locomotion, are sufficiently predictable (Chagnaud, Simmers et al. 2012).

Based on this consideration, a theoretical model was proposed that relates the relative influence of vestibular feedback vs. internal feedforward control on posture and gaze regulation to the quantifiable stereotype of head and body movements during locomotion (MacNeilage and Glasauer 2017). The model consequently suggests that the influence of feed-forward cues in balance and gaze control should increase with increasing stereotype, thus predictability of body and head movements, during locomotion.

It is as of yet not known whether a feedforward mechanism of postural control and gaze stability as observed in animal locomotion also exists in humans.

The aim of this thesis was to examine this hypothesis in two studies on healthy individuals and patients with a central ocular motor disorder (i.e., downbeat nystagmus).

(1) In the first study of this thesis (Dietrich, Heidger *et al*. 2020) we tested in healthy individuals the differential impact of an electrical vestibular stimulation on postural stability during standing and different walking modes. We then evaluated whether activity-dependent changes in the influences of the stimulation can be explained by the aforementioned model and thus are indicative for a feedforward regulation of balance control during human locomotion (Dietrich, Heidger *et al.*, 2020).

(2) In the second study (Dietrich, Pradhan *et al.* 2022) we evaluated whether analogous activity-dependent effects can be observed on gaze regulation during locomotion in a clinical population. In particular, we evaluated whether the intensity of central nystagmus in patients with downbeat nystagmus becomes modulated during locomotion in a manner that is compatible with the presence of a feedforward mechanism regulating gaze control during human locomotion.

2. Activity-dependent vestibular influence on balance and ocular-motor control

Stabile postural balance and locomotion can only be achieved by constant and accurate sensory feedback. Changes in the surrounding environment are detected by the peripheral receptors of the different sensory systems and conveyed to higher centers in the central nervous system. In the central nervous system, the various sensory inputs are processed and integrated into the motor output to increase efficiency of and implement changes to the locomotor pattern.

For example, during locomotion, this sensorimotor integration ensures postural equilibrium by adjusting the stepping pattern to the changing environmental conditions (Nashner 1980, Gandevia and Burke 1992). Interestingly it appears as though the impact of sensory information on the motor output is variable and depends on the executed activity.

Building on the first notion of Brandt (Brandt, Strupp *et al.* 1999), that the influence of vestibular feedback on locomotor control is dependent on the locomotion speed, Jahn (Jahn, Strupp *et al.* 2000) concluded, that vestibular feedback cues are differentially weighted in the central nervous system.

Accordingly, faster, more automatized locomotion modes exhibit a downregulation of vestibular influence on motor control (Jahn, Strupp *et al.* 2000). Supporting evidence was found in the observation that vestibular sensory perturbations or deprivation have a greater impact on postural balance and locomotion during slow walking compared to fast walking or running (Brandt, Strupp *et al.* 1999, Jahn, Strupp *et al.* 2001, Wuehr, Schniepp *et al.* 2013, Wuehr, Schniepp *et al.* 2014, Dietrich, Heidger *et al.*, 2020).

Additionally, the relative influence of sensory cues to motor control also appear to change in a phase-specific manner during the gait cycle (Rossignol, Dubuc *et al.* 2006).

This is reflected in the observation that the walking pattern is particularly susceptible to a sensory disturbance during specific periods of the gait cycle (Hollands and Marple-Horvat 1996, Zehr and Stein 1999, Bent, Inglis *et al.* 2004).
Recent experimental findings further suggest that gaze stabilization governed by vestibular feedback via the vestibulo-ocular-reflex is analogously subject to gait cycle phase and speed dependent modulations (Dietrich and Wuehr 2019).

Beyond vestibular balance and gaze regulation, additional findings emphasize that also visual (Hollands and Marple-Horvat 1996, Bent, Inglis *et al.* 2004) and proprioceptive (Zehr and Stein 1999, Bent, Inglis *et al.* 2004) feedback cues are subject to similar phase-dependent modulations.

These observations altogether suggest that the dynamic sensorimotor interactions reflect a general neuronal mechanism that integrates and gates feedback- and feedforward information depending on the executed activity to ensure stabile gaze and balance during human locomotion (Roy and Cullen 2004, Rossignol, Dubuc *et al.* 2006, Lambert, Combes *et al.* 2012, Straka, Simmers *et al.* 2018, Dlugaiczyk, Wühr and Straka, 2020).
A possible neurophysiological substrate for this was found in an amphibian animal model (Combes, Le Ray *et al.* 2008, Lambert, Combes *et al.* 2012). In this animal model, it was shown that during rhythmic and stereotyped tadpole swimming compensatory eye movements – which prevent retinal image slip to ensure visual acuity during head movements – are directly driven by locomotor efference copy signals, which are generated by the activity of spinal neuronal networks, generally referred to as central pattern generators (Lambert, Combes et al. 2012).
Previously it was assumed that compensatory eye movements are mainly initiated by the sensory feedback driven vestibulo-ocular-reflex and intrinsic feedforward mechanisms merely contribute in a synergistical way (Lambert, Combes et al. 2012). However there is evidence that these copies of spinal output actively and selectively suppress afferent sensory input (Lambert, Combes *et al.* 2012, von Uckermann, Le Ray *et al.* 2013, Dietrich, Heidger *et al.*, 2020). Furthermore these signals carry predictive information of the locomotor command and can directly control extraocular motor output and thus represent a feed-forward mechanism of gaze control (Lambert, Combes *et al.* 2012, von Uckermann, Le Ray *et al.* 2013, von Uckermann *et al.*, 2016).
Consequently, in humans an analogue feed-forward mechanism could be responsible for the speed and phase dependent modulation of sensory influence on balance and gaze control (Jahn and Wühr, 2020). During stereotype locomotor activities such an efference copy-based feed-forward mechanism could provide estimates of the resultant changes in head and body motion. Based on these estimates, compensatory ocular and postural reflexes could be quickly initiated to ensure gaze stabilization and dynamic postural stability.
However, a feed-forward regulation during human locomotion can only be efficient if the head and body motions occurring during locomotion are sufficiently stereotype and can thus be adequately internally predicted without afferent feedback (Chagnaud, Simmers *et al.* 2012).

Related to this assumption, a recently proposed theoretical model suggests that the influence of the locomotor efference copy-based feedforward mechanism of gaze and balance regulation can be related to the stereotype or predictability of the spatiotemporal coupling between trunk and head movements during locomotion – which can be quantified experimentally (MacNeilage and Glasauer 2017).

Experimental quantification of head and body motions during human locomotion further shows that their stereotype increases at faster locomotion modes (i.e. fast walking and running) and expresses variability within the gait cycle depending on the phase.

Hence, the model suggests that during activities with a high internal predictability of body and head movements, vestibular cues should be down-regulated that is suppressed, while the influence of an efference copy-based feed- forward mechanism should be up-regulated that is enhanced.

Consequently, tasks where the predictability of body and head movements is low, for example standing or slow walking, should depend more on vestibular input and less on efference copy-based feedforward mechanism (MacNeilage and Glasauer 2017, Dietrich, Heidger *et al*. 2020, Jahn and Wühr, 2020).

Therefore his model offers a reasonable explanation for the finding that the effect of an impairment or perturbation of the sensory system decreases with increased locomotor speed that has been observed and described in the past (see Figure 1) (Brandt, Strupp *et al.* 1999, Jahn, Strupp *et al.* 2000, Jahn, Strupp *et al.* 2001, Schneider, Jahn *et al.* 2008, Schniepp, Wuehr *et al.* 2012, Wuehr, Schniepp *et al.* 2013, Wuehr, Schniepp *et al.* 2014, Jahn and Wühr 2020, Dietrich, Heidger *et al.* 2020).

The model has, however, not yet been validated in humans.

The validation of this model was the purpose of the current thesis and pursued by two approaches:

(1) by relating the model predictions to the impact of an electrical vestibular stimulation on balance control during different activities in healthy individuals and

(2) by relating the model predictions to the impact of different activities on ocular-motor control in a clinical population of patients with downbeat nystagmus.

In the following the experimental paradigm (in particular the vestibular stimulation method) of the first study and the ocular-motor disorder (i.e. downbeat nystagmus) studied in the second study will be shortly introduced.

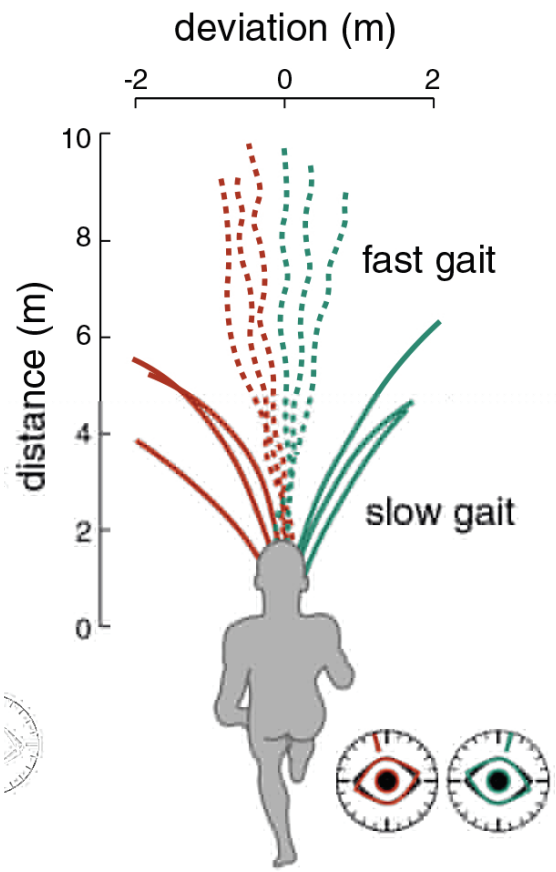

Figure 1: Speed dependent modulation of sensory (visual) feedback.

Comparison of visually induced gait deviations during slow and fast walking speeds. Visually induced direction-specific gait deviations from the intended straight-ahead path are achieved by using inverting prisms oriented 15° off the vertical roll plane during locomotion. Increased locomotion speeds exhibit a considerable decrease in lateral gait deviations.

3. Galvanic vestibular stimulation

Galvanic vestibular stimulation is a simple non-invasive method to externally modulate vestibular afferent signals (i.e., semicircular canal and otolith afferent signals) (Goldberg, Smith *et al.* 1984, Kim and Curthoys 2004, Kwan, 2016, Lajoie *et al.*, 2021). Therefor it has become a widely used, reliable and safe tool for studying the vestibular function in humans.

In a typical setup, a small amplitude galvanic current (around 2 mA) is delivered with two electrodes (anode and cathode) percutaneous, binaurally over the mastoid process (Pavlik, Inglis *et al.* 1999).

Once the galvanic current is applied, peripheral vestibular afferents are stimulated which in turn generate virtual head movement encoding signals (Kwan, 2016). These movement encoding signals are then processed in the central vestibular system and as a result evoke distinct postural, ocular and perceptual responses (Fitzpatrick and Day 2004). Through relating a measured motor response to the galvanic vestibular stimulation, the vestibular

influence on postural and ocular motor control can thus be experimentally examined.

Potential habituation to prolonged stimulation can be avoided by using a bandlimited stochastic vestibular stimulation profile that oscillates around zero within a chosen frequency band (Pavlik, Inglis *et al.* 1999).

When a stochastic vestibular stimulation is used, a cross-correlation and coherence analysis between the galvanic vestibular stimulation stimulus and the studied motor response (postural displacements or eye movements) can be performed to estimate the strength and timing of vestibulo-motor coupling in the time and frequency domain (see Figure 2) (Dietrich, Heidger *et al.* 2020).

It is worth mentioning that apart from its versatility in testing the vestibular system, galvanic vestibular stimulation, additionally shows promising results as an effective therapeutic tool in the treatment of patients with bilateral vestibulopathy, as recent research (Wuehr, Nusser *et al.* 2016) has shown.

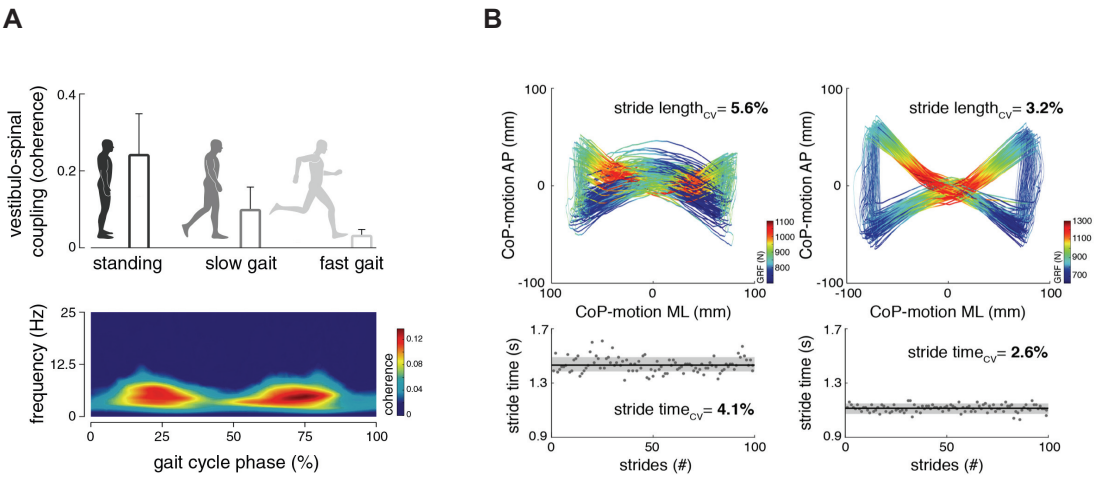

Figure 2: Phase- and Speed dependent influence of sensory (vestibular) feedback.

(A) Differential influence of a continuous stochastic galvanic vestibular stimulation on balance control in dependence of the speed and phase of the gait cycle. The influence of the external galvanic perturbation becomes considerably smaller while walking compared to standing. An increase in locomotion speeds is accompanied by a further decrease in vestibular influence. Furthermore, the up- and down-regulation of the vestibulo-spinal coupling depends on the gait cycle phase.

(B) Representative example of body sway during slow (left) and fast (right) locomotion in a patient with bilateral vestibulopathy. The irregularity of the center of pressure (COP) trajectories (upper panel) and the stride time variability is strongly pronounced during slow walking versus fast walking. Faster locomotion leads to a considerable reduction in gait instability

4. Downbeat nystagmus

In general nystagmus refers to involuntary repetitive eye movement patterns that consist of a slow phase (pursuit) followed by a quick phase (resetting saccade). The nystagmus is named according to the direction of the quick phase (e.g., downbeat nystagus).
Nystagmus is categorized into physiological and pathological forms. A physiological nystagmus occurs for example during rotational movements of the head (vestibular nystagmus) or movement of the visual surrounding (optokinetic nystagmus) to counteract retinal image slip and maintain stable gaze. The pathological nystagmus results from a central or peripheral ocular-motor dysfunction.
In downbeat nystagmus the pathological vertical eye-movements are a result of a central ocular-motor dysfunction (Strupp, Kremmyda *et al.* 2014). Here the pattern of the pathological eye-movements generally consists of involuntary upward directed slow phases followed by downward directed resetting saccades (Wagner, Glaser *et al.* 2008, Strupp *et al.*, 2014) , hence the name downbeat nystagmus.
Downbeat nystagmus is considered to be a form of fixation nystagmus with the intensity of the nystagmus typically depending on the direction of the gaze (horizontal left/right and downwards directed gaze generally increase the nystagmus) (Wagner, Glaser *et al.* 2008, Strupp *et al.*, 2014) .
Besides nystagmus, postural instability is another key symptom that typically accompanies downbeat nystagmus (Schniepp, Wuehr *et al.* 2014, Leigh and Zee 2015). Therefore patients with downbeat nystagmus regularly report unsteadiness of gait, dizziness, vertigo and blurred vision or ‘bouncing images’ (i.e., oscillopsia) (Strupp, Kremmyda *et al.* 2014).

With an overall diverse ethological spectrum, roughly 60% of patients show secondary forms of downbeat nystagmus with cerebellar dysfunction being the most frequent cause (Wagner, Glaser *et al.* 2008, Schniepp, Wuehr *et al.* 2014). In roughly 40% of the patients, no underlying cause can be identified (i.e. idiopathic downbeat nystagmus).

Thus, so far the exact pathomechanisms and origin of downbeat nystagmus is still unknown. Nevertheless, it is commonly accepted that downbeat nystagmus is closely associated with cerebellar impairments and dysfunctions in regions of the vestibulo-cerebellum.
In line with that, supporting evidence was detected with the help of brain imaging of patients with downbeat nystagmus, that showed a reduced activation and metabolism in the cerebellar flocculus and the paraflocculus accompanied by a localized reduction of grey matter in the vermis and the lateral cerebellum (see Figure 3) (Kalla, Deutschlander *et al.* 2006, Hüfner, Stephan *et al.* 2007, Schniepp, Wuehr *et al.* 2014).

Lesions within the vestibulo-cerebellum typically lead to impaired integration of vestibular information for eye movement control during head movements and coordination of the limbs

and body during walking and standing (Kandel, Schwartz *et al.* 2000) and thus account for the above mentioned ocular-motor and postural symptoms.

According to Hüfner (Hüfner *et al.*, 2007), loss or reduction of inhibitory cerebellar Purkinje cell activity presents an explanation for the ocular-motor dysfunction in downbeat nystagmus. Furthermore the computational model by Marti (Marti *et al.*, 2008) showed that decreased floccular Purkinje cell activity results in eye movement patterns that are characteristic in downbeat nystagmus.

The central role of Purkinje cell activity is also reflected in the current, symptomatic pharmacological treatment of downbeat nystagmus.
A class of drugs that is known to act on Purkinje cell activity (i.e. 3,4-diaminopyridine, 4-aminopyridine and Chlorzoxazone) have been shown to effectively suppress nystagmus, improve visual acuity and postural symptoms in patients with downbeat nystagmus (Strupp, Schüler *et al.* 2003, Feil, Claaßen *et al.* 2013, Kalla *et al.*, 2016).

Downbeat nystagmus symptoms can not only be influenced by medication but also exhibit a dependency on a variety of other factors. For instance, eccentric gaze, head orientation, resting periods and daytime have a modulating effect on ocular-motor symptoms in patients with downbeat nystagmus (Spiegel, Rettinger *et al.* 2009, Spiegel, Kalla *et al.* 2010, Spiegel, Claassen *et al.* 2016).

In direct relation to the topic of this thesis, downbeat nystagmus symptoms have been further shown to be dependent on the motor activity that is being executed.
Accordingly, postural instability in patients with downbeat nystagmus is characterized by a staggering, broad-based ataxic gait. These postural symptoms are aggravated during slow walking but steadily improve with increasing locomotion speed.
These observations are indicative of the presence of a feed-forward regulation of posture that increasingly suppresses dysfunctional sensorimotor balance reflexes at fast locomotion (Schniepp, Wuehr *et al.* 2014).
It is as of yet not known whether ocular-motor symptoms in downbeat nystagmus (in particular the central nystagmus) show a similar pattern of activity-dependence during locomotion.

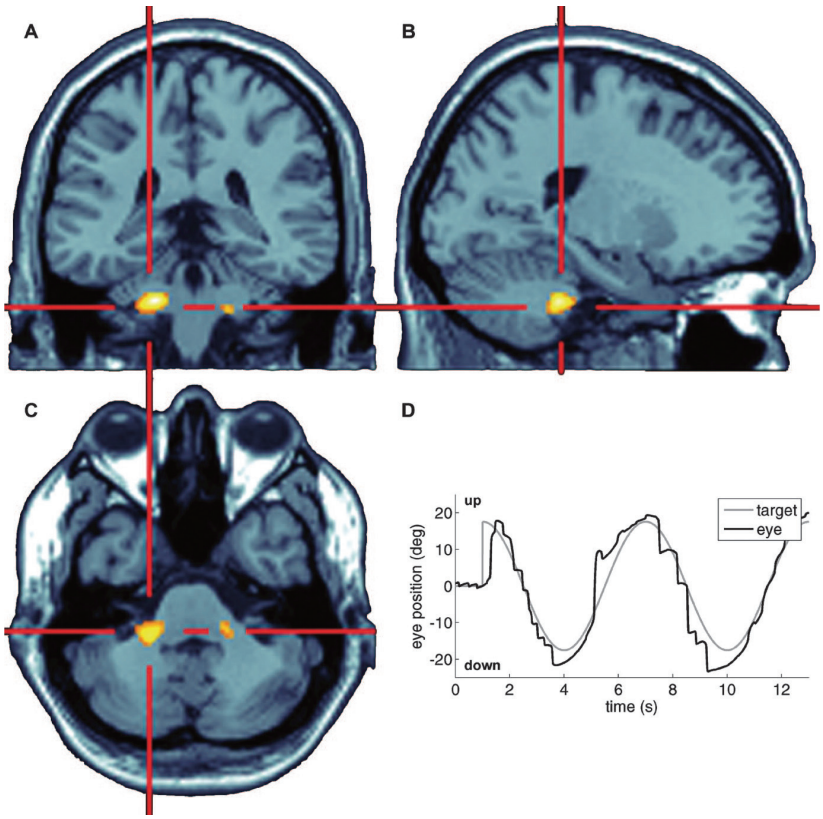

Figure 3: fMRI of floccular activity during vertical smooth pursuit eye movements in healthy subjects versus patients with downbeat nystagmus (DBN)

(A: coronal plane, B: sagittal plane, C: axial plane). Compared to the healthy subjects, patients with DBN exhibit a significant reduction of activation of both floccular lobes during downward but not upward pursuit. These findings support the assumption, that impaired downward pursuit in DBN is being caused by floccular dysfunction. (D) Exemplary eye position recording (search coil) of a patient with DBN during vertical pursuit.

5. Cumulative thesis

There is increasing evidence of activity-dependent changes of sensory contributions to motor control in human balance and gaze control during locomotion.

It has been hypothesized that this modulation reflects a selective gating of sensory feedback versus feedforward (i.e. efference copy based) mechanisms as observed during animal locomotion.

It is yet not known whether an analogue feed-forward mechanism exists in human locomotor control. However, recently MacNeilage and Glasauer (MacNeilage and Glasauer, 2017)

proposed a theoretical model that makes experimentally verifiable predictions based on the assumptions of said feed-forward mechanism of balance and gaze stability during human locomotion.

The objective of this thesis was the experimental validation of the model predictions in two separate studies on healthy individuals and patients with downbeat nystagmus:

1. The first study evaluated in a cohort of healthy individuals whether the differential effect of a galvanic vestibular stimulation on balance regulation during different motor activities is compatible with the model predictions.

2. The second study examined in a cohort of patients with downbeat nystagmus whether ocular-motor symptoms in these patients become modulated during locomotion and if this modulation is compatible with the model predictions.

In the first study with the title ‘Head motion predictability explains activity-dependent suppression of vestibular balance control’ we examined whether the differential impact of vestibular feedback cues on balance control during still stance and at different locomotion speeds can be explained by concurrent changes of the stereotype and hence predictability of head movements (Dietrich, Heidger *et al.* 2020). For this purpose, we experimentally estimated in healthy individuals (N=10) the gain of vestibulospinal balance reflexes during different motor activities by means of a galvanic vestibular stimulation and statistically related these estimates to the stereotype of, in parallel measured, head movements.

In the second study with the title ‘Downbeat nystagmus becomes attenuated during walking compared to standing’ we examined the intensity of nystagmus in patients with downbeat nystagmus (N=10) during standing compared to walking and evaluated whether modulations in nystagmus intensity between activities as well as during the gait cycle phases are compatible with the predictions of the theoretical model of a feed-forward mechanism regulating gaze control during human locomotion.

6. Publications

6.1. Publication I: “Head motion predictability explains activity-dependent suppression of vestibular balance control”

SCIENTIFIC REPORTS
nature research

OPEN

Head motion predictability explains activity-dependent suppression of vestibular balance control

H. Dietrich[1,5], F. Heidger[2,5], R. Schniepp[1,2], P. R. MacNeilage[1,3], S. Glasauer[1,4] & M. Wuehr[1*]

Vestibular balance control is dynamically weighted during locomotion. This might result from a selective suppression of vestibular inputs in favor of a feed-forward balance regulation based on locomotor efference copies. The feasibility of such a feed-forward mechanism should however critically depend on the predictability of head movements (HMP) during locomotion. To test this, we studied in 10 healthy subjects the differential impact of a stochastic vestibular stimulation (SVS) on body sway (center-of-pressure, COP) during standing and walking at different speeds and compared it to activity-dependent changes in HMP. SVS-COP coupling was determined by correlation analysis in frequency and time domains. HMP was quantified as the proportion of head motion variance that can be explained by the average head trajectory across the locomotor cycle. SVS-COP coupling decreased from standing to walking and further dropped with faster locomotion. Correspondingly, HMP increased with faster locomotion. Furthermore, SVS-COP coupling depended on the gait-cycle-phase with peaks corresponding to periods of least HMP. These findings support the assumption that during stereotyped human self-motion, locomotor efference copies selectively replace vestibular cues, similar to what was previously observed in animal models.

The vestibular system encodes head orientation and motion to facilitate balance reflexes that ensure postural equilibrium during passive as well as self-initiated movements[1]. During locomotion, i.e., stereotyped self-motion, vestibular influences on balance control appear to be dynamically up- or down-regulated in dependence on the phase and speed of the locomotor pattern. Accordingly, vestibulospinal reflexes exhibit phasic modulations across the locomotor cycle[2,3] with the result that balance is particularly sensitive to vestibular perturbations at specific phases of the gait cycle[4]. Furthermore, vestibular influences appear to be down-weighted during faster locomotion. Accordingly, the destabilizing impact of a vestibular loss or perturbation on the gait pattern decreases with increasing locomotion speeds[5–9].

It was previously assumed that activity-dependent modulations of vestibular balance reflexes might reflect an up- or down-regulation of a concurrent intrinsic feed-forward control of posture[10–13]. Accordingly, balance adjustments during self-motion might not solely rely on sensory feedback about how the body has moved, but also on predictions of resultant movements derived from efference copies of the motor command[14]. Physiological evidence for such a direct feed-forward control mode has recently been shown for animal locomotion. During *Xenopus laevis* tadpole swimming, intrinsic efference copies of the locomotor command deriving from spinal central pattern generators (CPG) were shown to directly trigger ocular adjustments for gaze stabilization and selectively cancel out any afferent (ex- and reafferent) vestibular inputs[10,15]. Thus, also during human stereotyped locomotion, efference copies might provide estimates of resultant head motion and assist or even substitute vestibular feedback cues in gaze and balance regulation. The feasibility of such a direct feed-forward mechanism should however critically rely on the predictability or stereotypy of head movements during locomotion[16].

Following this intuition, a statistically optimal model was recently proposed, that relates an empirically quantified metric (i.e., the kinematic predictability metric) of head motion predictability to the relative weighting of vestibular vs. motor efference copy cues in gaze and balance regulation during locomotion[12]. According to the model, activities linked to less stereotyped head movements should be more dependent on vestibular cues than

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activities with highly predictable head motion patterns. Likewise, timepoints during the stride cycle when head movement is less stereotyped should exhibit more vestibular dependence. To assess this hypothesis, we examined whether activity-dependent modulations of vestibular balance reflexes can be explained by alterations in the predictability of head movements. Modulations in vestibular balance control during different activities, i.e., standing as well as slow or faster walking, were studied by analyzing the differential impact of a continuous stochastic vestibular stimulation (SVS) on body sway (i.e., center-of-pressure-displacements, COP) in the frequency (coherence) and time (cross-correlation, phase) domain. In parallel, we quantified the predictability of head kinematics associated with these activities and related this metric to an estimate of relative sensory weight.

Using this theoretical and evidence-based approach we aimed to evaluate three hypotheses concerning the role of vestibular cues in balance regulation: (1) Compared to quiet standing, vestibular influence on balance control should decrease during walking due to the presence of a locomotor efference copy; (2) it should be further down-regulated with faster locomotion due to increasingly stereotyped head kinematics during faster locomotion; (3) phasic modulations of vestibular balance reflexes across the gait cycle should correspond to phase-dependent alterations in head motion predictability.

Methods

Subjects. Ten healthy subjects (mean age 29.3 ± 3.7 years, 3 females) participated in the study. None of the participants reported any auditory, vestibular, neurologic, cardio-vascular or orthopedic disorders. All subjects had normal or corrected-to-normal vision. Each participant gave written informed consent prior to the experiments. The Ethics Committee of the University of Munich approved the study protocol, which was conducted in conformity with the Declaration of Helsinki.

Galvanic vestibular stimulation. Galvanic vestibular stimulation uses the external application of electrical current to modulate semicircular canal and otolith afferent activity in the vestibular endorgans[17–19]. A pair of conductive rubber electrodes was attached bilaterally over the left and right mastoid process behind the ears. A stochastic galvanic vestibular stimulation (SVS) delivered via this electrode configuration with the head facing forward primarily elicits a postural roll response in the frontal plane[20,21]. Before electrode placement, the skin surface at the electrode sites was cleaned and dried, and a layer of electrode gel was applied before electrode placing to achieve uniform current density and minimize irritation to the skin during stimulation. The SVS profile consisted of a bandwidth-limited stochastic stimulus (frequency range: 0–25 Hz, peak amplitude ±4.5 mA, root mean square (RMS) 1.05 mA) delivered via a constant-current stimulator (Model DS5, Digitimer, Hertfordshire, UK). The stimulus bandwidth (0–25 Hz) was chosen to cover the entire frequency response bandwidth of vestibular-induced modulations in lower limb muscle activity[2,3].

Test procedures. Each participant stood and walked on a pressure-sensitive treadmill (Zebris®, Isny, Germany; h/p/cosmos®, Nussdorf-Traunstein, Germany; 1.6 m long; sampling rate of 100 Hz). Five different conditions were tested in randomized order: three stimulation conditions with continuous SVS and two non-stimulation conditions. SVS was presented during 180 s of quiet standing, as well as during slow walking at 0.4 m/s and medium walking at 0.8 m/s, each for 600 s. Head movements without SVS stimulation were recorded during walking at 0.4 and 0.8 m/s, each for 300 s. Walking was guided by a metronome with a cadence of 52 steps/min for the slow and 78 steps/min for the medium walking speed, respectively. Walking speeds and cadences were chosen in order to allow direct comparison with previous studies[2,3,22]. During trials, participants were instructed to fixate on a target located 3 m in front of them at eye level. Before each recording, participants were given 30 s to acclimatize to the preset treadmill speed and walking cadence. Between trials, participants were given at least two minutes to recover.

Data analysis. *Center-of-pressure displacements, head kinematics, and gait parameters.* For each stance and walking trial, the continuous trajectory of the center-of-pressure (COP) was computed as the weighted average of the pressure data recorded from the treadmill by using the standard method for determining the barycenter (*sum of mass* × *position*)/*sum of mass*[23]. COP motion was analyzed in the medio-lateral (ML) dimension, i.e., the primary dimension of postural responses induced by binaural bipolar SVS[20]. Head kinematics in ML dimension (i.e., linear head acceleration in the ML dimension and angular head velocity in the roll plane) were measured with an inertial measurement unit (IMU) containing a triaxial accelerometer and gyroscope (APDM, Inc., Portland, OR, sampling rate of 128 Hz), strapped to the forehead. Furthermore, for each walking trial, the following spatiotemporal gait parameters were analyzed: base of support, stride length, stride time, single support percentage, and double support percentage, as well as the coefficient of variation (CV) of each of these parameters.

Cross-correlation and coherence analysis. For all stimulation trials, correlation analysis in the frequency (coherence) and time (cross-correlation, phase) domain was used to estimate the average SVS-induced variations in COP-displacements. Analysis was performed for the first 180 s of each recording to yield an equal amount of analyzed data points for the stance and walking trials. Since coherence is normalized by the power in both SVS- and COP-signals, it is particularly suitable to compare SVS-COP coupling across different activities that are linked to different magnitudes of COP-displacements. Coherence estimates with confidence limits were computed based on the auto-spectra of the SVS and COP signals ($P_{AA}(f)$ and $P_{BB}(f)$ respectively) as well as the cross-spectrum ($P_{AB}(f)$) using a finite fast Fourier transform with a block size of 2 s resulting in a frequency resolution of 0.5 Hz[24]:

$$C_{AB}(f) = \frac{|P_{AB}(f)|}{P_{AA}(f)P_{BB}(f)}$$

This yielded a 95% confidence limit for coherence estimates of 0.033[24]. The resultant coherence estimate is a unitless measure bounded between 1 (indicating a perfect linear relationship at the absence of noise) and 0 (indicating independence between the two signals).

Cross-correlations between SVS and COP signals were computed to determine the onset and peak of SVS-induced COP displacements. For this purpose, the inverse Fourier transform of the cross-spectrum $P_{AB}(f)$ was computed and normalized by the norm of the input and output vectors to obtain unitless correlation values bounded between -1 and 1[2]. The resultant 95% confidence limit for cross-correlation estimates was 0.015. Finally, phase estimates between the SVS and COP signals were estimated from the complex valued coherence function. This allows to determine the phase lag corresponding to frequency bandwidths with significant SVS-COP coherence estimates[25]. The slope of the phase values over the range of significant coherence estimates was computed using regression analysis and multiplied by $1000/2\pi$ to yield an estimate of the phase lag in milliseconds.

For the two walking stimulation trials, we further analyzed phasic modulations in the correlation between SVS and COP signals across the average gait cycle, using time-dependent coherence analysis according to a previously described procedure[2,3] First SVS and COP signals were cut into individual strides synchronized to the left heel strike and then time-normalized by resampling each stride to a total of 300 samples. The first 250 strides of each trial were taken for further analysis and padded at the start and end with data from the previous and subsequent strides to avoid distortions in the subsequent correlation analysis. Time-dependent coherence was then estimated using a Morlet wavelet decomposition based on the method of Zhan *et al.*[26], with a resultant frequency resolution of 0.5 Hz and 95% confidence limits of 0.018.

Head motion predictability. Head motion predictability (HMP) was quantified separately for linear head acceleration and angular head velocity recorded during the non-stimulation conditions according to a previously proposed procedure[12]. First, IMU signals were cut into individual strides synchronized to the left heel strike and further time-normalized by resampling each stride to a total of 300 samples. Head motion data from the first 125 strides ($N = 125$) was used for further analysis and averaged to reconstruct the mean head motion trajectory across the stride cycle, i.e., the stride-cycle attractor. Subsequently, the total variance SS_{tot} and residual variance SS_{res} of head motion were calculated:

$$\begin{aligned} SS(t)_{tot} &= \frac{1}{N}\sum_{i=1}^{N}(h(t)_i - \bar{h})^2 \\ SS(t)_{res} &= \frac{1}{N}\sum_{i=1}^{N}(h(t)_i - f(t))^2 \end{aligned}$$

where $h(t)_i$ is the head motion during the i th stride at the normalized stride time t, $\bar{h}$ is the average head motion over all stride cycle phases and strides, and $f(t)$ denotes the stride cycle attractor. Correspondingly, SS_{tot} quantifies the signal deviation from the overall mean signal whereas SS_{res} gives the signal deviation from the stride cycle attractor.

Using these metrics, the proportion of head motion variance that can be explained by the stride cycle attractor, i.e., explained variance ($V_{exp} = 1 - SS_{res}/SS_{tot}$), and the proportion of residual head motion variance $V_{res} = SS_{res}/SS_{tot}$ can be derived. Low values of V_{res} indicate a high HMP. Hence, knowing the exact stride cycle phase, feed-forward signals of the locomotor command can provide reliable information about the most likely ongoing movement. However, as V_{res} increases, head motion prediction based on stride cycle phase information becomes less accurate and additional sensory cues are required for head motion estimation. These considerations can be expressed in the form of a statistically optimal model (in the sense of obtaining the lowest-variance estimate), i.e., the maximum likelihood estimation model for cue integration[27]. Accordingly, head motion $\hat{H}$ can be estimated by a weighted linear combination of vestibular (sensory, S) and efference copy (motor, M) cues with weights w_{sens} and w_{mot} corresponding to the relative reliability of these cues:

$$\begin{aligned} \hat{H} &= w_{sens}S + w_{mot}M \\ w_{sens} &= \frac{\sigma_{mot}^2}{\sigma_{sens}^2 + \sigma_{mot}^2} \qquad w_{mot} = \frac{\sigma_{sens}^2}{\sigma_{sens}^2 + \sigma_{mot}^2} \end{aligned}$$

The above weights can now be estimated using the head motion data based on the following two assumptions: (1) According to Weber's law, sensory noise is assumed to be signal-dependent, i.e., its variance should be proportional to the squared signal[28]. As the average signal is approximately zero for oscillatory locomotor movements, sensory noise can be estimated by $\sigma_{sens}^2 = kSS_{tot}$, with the Weber's fraction k. (2) If the intended head motion during each stride equals the stride cycle attractor, motor noise can be estimated as $\sigma_{mot}^2 = SS_{res}$. According to Fitt's law, motor noise is assumed to increase with faster movement velocities[29–31]. Note, that this estimate of σ_{mot}^2 represents an upper limit of motor noise since in this estimate any deviation from the gait cycle attractor including intentional deviations (e.g. head turns) are interpreted as motor noise. Thus, the actual motor noise is likely to

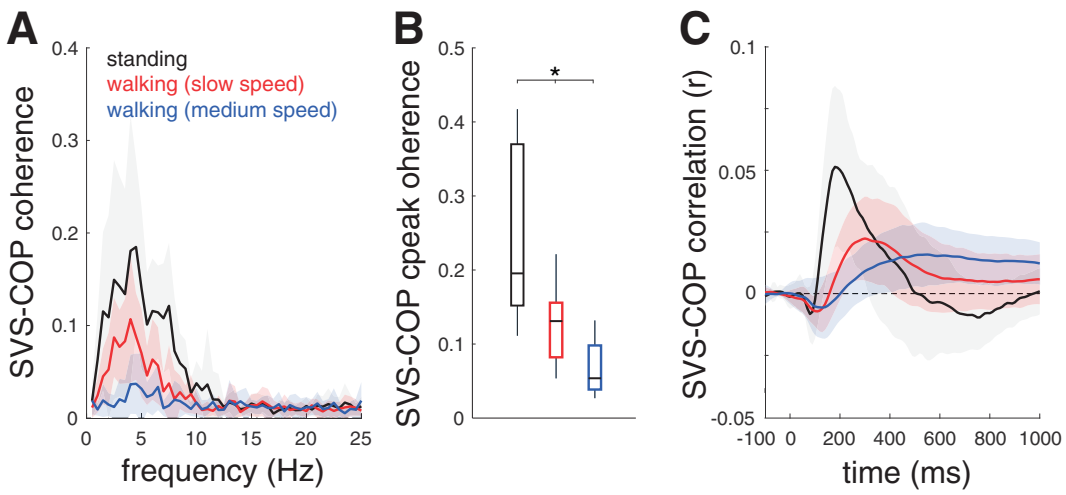

Figure 1. Correlation analysis in frequency and time domain for coupling between SVS and COP displacements during different activities. (**A**) Coherence functions, (**B**) peak coherence values, and (**C**) corresponding cross-correlations between SVS and COP displacements. SVS-COP coherence drops from standing to slow walking and is further reduced at faster walking speed. SVS-induced COP displacements exhibit a short latency response around 80–120 ms and a medium latency response of opposite polarity at around 200–290 ms. *Indicates a significant difference. *SVS: stochastic vestibular stimulation; COP: center-of-pressure.*

be lower than this estimate. Based on these assumptions, sensory weight can by expressed as directly proportional to V_{res}:

$$w_{sens} = \frac{SS_{res}}{k * SS_{tot} + SS_{res}} * \frac{1/SS_{tot}}{1/SS_{tot}} = \frac{V_{res}}{V_{res} + k}$$

Statistical analysis. Data are reported as mean ± SD. The effects of correlation analysis parameters, head predictability estimates, and gait parameters were analyzed using a repeated-measures analysis of variance (rmANOVA) and Bonferroni post hoc analysis with condition (standing, slow and medium walking) as factor. Results were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS (Version 25.0; IBM Corp., Armonk, NY).

Results

All participants exhibited significant correlations between SVS and COP displacements in both the frequency and time domain. SVS-COP overall coherence within the 0–25 Hz bandwidth peaked at 4.8 ± 1.4 Hz for standing (COP RMS: 10.9 ± 7.4 mm), 3.9 ± 0.8 Hz for slow (COP RMS: 62.6 ± 8.6 mm), and 4.6 ± 2.4 Hz for medium (COP RMS: 60.7 ± 10.8 mm) walking speed ($F_{2,18} = 1.2$; $p = 0.526$; Fig. 1A). Peak coherence dropped from standing to slow waking and further decreased with faster walking ($F_{2,18} = 22.6$; $p < 0.001$; Fig. 1B). Cross-correlation analysis revealed a short latency component of SVS-induced COP responses at 85 ± 11 ms for standing and slightly later responses for slow (112 ± 12 ms) and medium (111 ± 9 ms) walking speeds ($F_{2,18} = 54.1$; $p < 0.001$). A medium latency response of opposite polarity occurred at 203 ± 45 ms for standing and slightly later for slow (273 ± 18 ms) and medium (273 ± 25 ms) walking speeds ($F_{2,18} = 21.7$; $p = 0.001$; Fig. 1C). Phase lags at frequency bandwidth with significant coherence estimates corresponded to the medium latency response with 204 ± 44 ms for standing, and 267 ± 21 ms for slow, and 275 ± 22 ms for medium walking speed ($F_{2,18} = 24.0$; $p < 0.001$).

Similar to global coherence estimates, time-frequency analysis of SVS-COP coupling across the gait cycle revealed a drop of peak coherence from slow to medium walking speed ($F_{1,9} = 15.5$; $p < 0.001$, Fig. 2A–C). Analysis of HMP revealed a corresponding decrease in mean head motion V_{res} (i.e., an increase in HMP) from slow to medium walking speed for both linear head acceleration and angular head velocity ($F_{1,18} = 14.0$; $p = 0.001$, Fig. 2A–C). Furthermore, HMP was generally higher for linear head acceleration compared to angular head velocity ($F_{1,18} = 44.7$; $p < 0.001$, Fig. 2C). SVS-COP coupling across the gait cycle exhibited phasic modulations with two distinct peaks occurring at 25.0 ± 2.4% and 74.3 ± 2.7% of the gait cycle during slow walking and at 25.4 ± 1.4% and 76.6 ± 1.4% of the gait cycle during walking at medium speed (Fig. 2A,B). In accordance, the estimated HMP was similarly modulated throughout the gait cycle. Periods of maximum V_{res} (i.e., least predictability) of angular head velocity corresponded to peaks of SVS-COP coherence (at 21.6 ± 2.8% and 73.5 ± 3.1% of the gait cycle during slow walking and 21.3 ± 1.3% and 73.4 ± 2.6% of the gait cycle during medium walking). In contrast, peaks of linear head acceleration V_{res} occurred at considerably earlier instances of the gait cycle (5.9 ± 2.8% and 56.4 ± 1.0% of the gait cycle during slow walking and 6.7 ± 2.9% and 56.9 ± 1.4% of the gait cycle during medium walking).

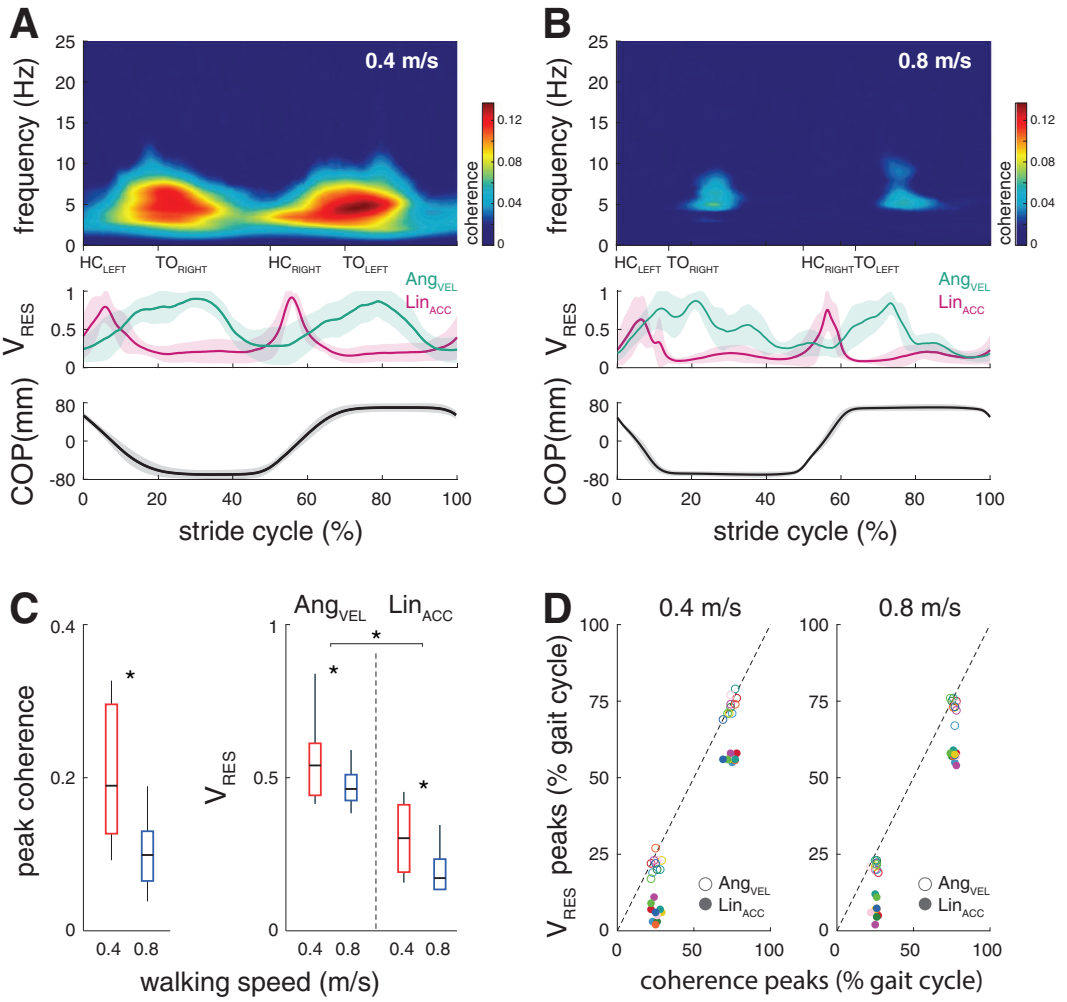

Figure 2. Time-frequency analysis of coupling between SVS and COP displacements and corresponding estimates of head motion predictability. (**A,B**) Average time-dependent coherence between SVS and COP at slow and medium walking speed (upper panels), corresponding average head motion V_{res} curves (middle panels), and COP motion (lower panels) in dependence on the gait cycle phase. (**C**) Peak coherence and corresponding average V_{res} for angular head velocity and linear head acceleration. (**D**) Temporal correspondence between phase-dependent peaks in SVS-COP coherence and peaks in head motion V_{res} at slow and medium walking speed. Both SVS-COP coupling and head motion predictability decrease with faster locomotion and are phase-dependently modulated across the gait cycle. SVS-COP coupling exhibits two peaks across the stride cycle that correspond well to periods of highest V_{res} (i.e., least predictability) of angular head velocity. *Indicates a significant difference. *SVS: stochastic vestibular stimulation; COP: center-of-pressure; V_{RES}: residual variance; Ang_{VEL}: angular head velocity; Lin_{ACC}: linear head acceleration; HC: heel contact; TO: toe off.*

Continuous SVS did not affect the average spatiotemporal walking pattern but resulted in a considerable increase of stride-to-stride variability (i.e., increased CV) of all analyzed gait parameters (Fig. 3B). This effect was diminished during medium compared to slow walking for the CV of stride time ($F_{1,9} = 5.9$; $p = 0.038$), single support percentage ($F_{1,9} = 7.7$; $p = 0.022$), and double support percentage ($F_{1,9} = 5.9$; $p = 0.038$).

Discussion

Here we observed that activity-dependent modulations of vestibular influence on balance control closely match differences in head motion predictability (HMP). This finding supports a previously proposed model[12], based on the idea that during stereotyped locomotion, efference copies of locomotor commands may be used in conjunction with sensory, especially vestibular, cues in order to estimate resultant head movements and trigger adequate balance adjustments. The extent to which balance regulation during locomotion relies on concurrent vestibular vs. motor feed-forward signals should further depend on the reliability of these estimates, such that higher weighting is given to the less noisy estimate[27]. Accordingly, we found that activities linked to less stereotyped head movements (i.e., standing or slow walking) were more sensitive to externally triggered vestibular cues than activities with highly predictable head motion patterns (i.e., faster walking). Furthermore, we found that during walking, sensitivity to SVS was highest at the times of lowest HMP. Thus, the present results provide a reasonable explanation for the dynamic weighting of vestibular influences across and within different activities and further

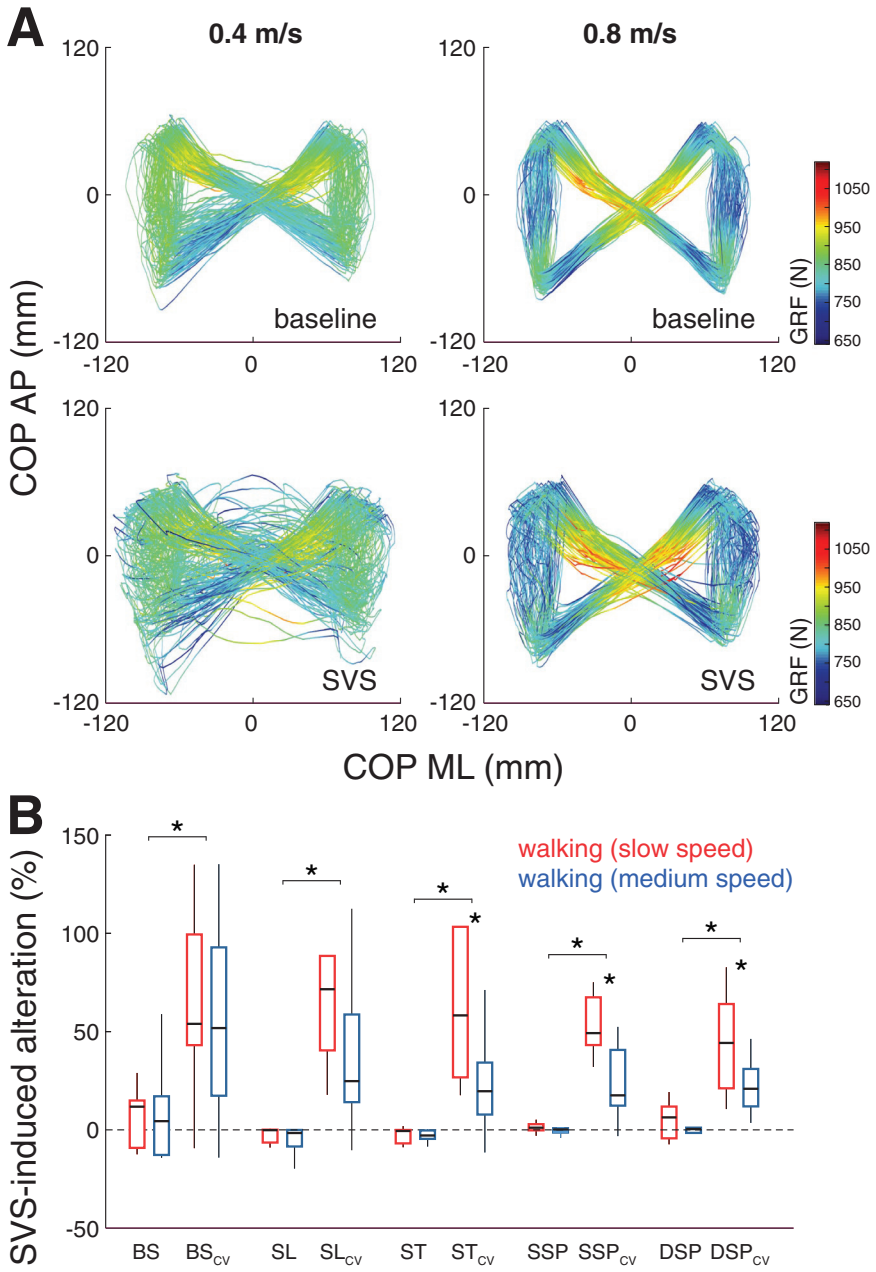

Figure 3. Effects of SVS and walking speed on spatiotemporal gait parameters. (**A**) Representative examples of COP trajectories during slow (left) and medium (right) walking speed for trials without stimulation (upper panel) and with continuous SVS (lower panel). (**B**) Percentage differences in gait parameters for walking with continuous SVS compared to baseline walking at the two locomotor speeds. SVS does not affect the mean gait pattern but induces increased stride-to-stride fluctuations (i.e., increased CV values) in all gait parameters. This effect diminishes with faster locomotion. * Indicates a significant difference. *SVS: stochastic vestibular stimulation; COP: center-of-pressure; BS: base of support; SL: stride length; ST: stride time; SSP: single support percentage; DSP: double support percentage; CV: coefficient of variation.*

emphasize the possibility of an intrinsic feed-forward regulation of balance during human locomotion based on locomotor efference copies. In the following, we will discuss these findings with respect to their functional implications and possible physiological correlates.

The influence of externally triggered vestibular cues on body sway (i.e., SVS-COP coherence) was attenuated during walking compared to standing (Fig. 1). This agrees with the recently reported decrease of vestibular influence on body balance after gait initiation and the corresponding increase after gait termination[32]. Such general down-weighting of vestibular influence during locomotion is consistent with predictions of the model employed here. During locomotion, the presence of an efference copy of locomotor commands imposes an upper limit for the weighting of sensory influences, i.e., $w_{sens} < 1/(1 + k) < 1$, which depends on the Weber's fraction k, the proportionality constant for signal dependent noise[12]. Thus, balance regulation during locomotion will always be

partially governed by a locomotor efference copy, i.e., $w_{mot} > 0$. Previous literature indicates that the attenuation of balance-related vestibular reflex gains during locomotion is a more general phenomenon that also concerns vestibulo-ocular reflex pathways[33,34]. Accordingly, it was shown in patients with a unilateral vestibular failure that spontaneous nystagmus resulting from a vestibular tone imbalance is considerably dampened during ambulation[35]. A complete suppression of the horizontal vestibulo-ocular reflex has been demonstrated in tadpole swimming, i.e., a locomotor activity where the spatiotemporal coupling between rhythmic propulsive locomotor movements and resultant head displacements is high[10,16]. Similar effects were also observed in other non-vestibular sensory modalities. For instance, proprioceptive stretch reflexes that govern postural control during standing are known to be selectively suppressed during locomotion[36]. This does not mean that static postural control is purely governed by sensory feedback regulation. Feed-forward postural adjustments are well documented for both voluntary self-initiated and predictable external balance perturbations[37]. However, it is still controversially discussed whether and to what extent feed-forward control also governs static undisturbed balance regulation[38].

During locomotion, vestibular feedback is thought to be essential for the maintenance of dynamic stability by fine-tuning the timing and magnitude of foot placement[2,4,8]. In line with this, significant SVS-COP coupling during locomotion led to an increased spatiotemporal variability of stride-to-stride walking movements despite the otherwise unaffected average gait parameters (Fig. 3). Both SVS-COP coupling and increased stride-to-stride variability decreased from slow to medium walking speed (Figs. 1–3). This observation is in line with previous studies reporting that the destabilizing impact of a vestibular loss or external vestibular perturbation becomes considerably attenuated with increased locomotor velocity and cadence[3,5,7,9]. Moreover, we found that SVS-COP coupling was phase-dependently modulated during locomotion, exhibiting two consistent peaks across the gait cycle with equal timing for both examined walking speeds. Both speed- and phase-dependent changes in SVS-COP coupling closely matched concomitant changes in HMP (Fig. 2). Accordingly, V_{res} of linear acceleration and angular velocity of head motion decreased with faster locomotion (i.e., increased predictability) and consistently exhibited two local maxima across the gait cycle (i.e., least predictability). These phase-dependent changes of HMP in the ML dimension show a substantial temporal agreement with previously reported modulations of vestibulo-muscular coupling across the locomotor cycle, in particular for muscle groups that mediate ML body sway[2,3]. It is yet unclear, whether the coincidence between modulations in SVS-COP coupling and HMP observed during symmetric steady-state walking continues to exist during asymmetric walking modes (e.g., split-belt walking or walking along a curved path), where vestibulo-muscular coupling has been shown to be independently modulated in each limb[39]. Finally, phasic modulation of SVS-COP coupling across the locomotor cycle temporally matched modulations of V_{res} of angular head velocity rather than of linear head acceleration. This suggests that the observed SVS-induced COP displacements primarily reflect responses to activation of semicircular canal afferents. In line with this, medium-latency body sway responses at the frequency bandwidth and phase lags observed in the present study were previously shown to most likely reflect semicircular canal afferent responses to galvanic vestibular stimulation[40,41].

Previous reports hypothesized that the activity-dependent modulation of vestibular feedback during locomotion is reflected by concurrent changes in muscle activation or foot placement patterns to stabilize posture[2–4]. Others have proposed that vestibular down-regulation during faster locomotion simply occurs due to a larger degree of automated behavior[5] or biomechanical stability[32] that tends to rely less on sensory feedback. Besides, the rapid stepping patterns at faster locomotion might impose too short time frames for an adequate operation of vestibular balance reflexes with latencies of about 50–60 ms[42]. However, even at fast running with gait cycle durations of about 600 ms[43], vestibulospinal reflexes should be fast enough to efficiently stabilize posture. The present findings suggest that, besides automation, stability, or time-constraints, changes in HMP play an important role in defining the activity-depended modulation of vestibular control of balance during locomotion. Accordingly, despite the increase of sensory and motor noise linked to faster movements[28,29,44] the relative ratio of sensory vs. motor noise does not remain constant but appears to become greater with increasing locomotion speed. The relative increase in sensory noise should lead to a down-weighting of vestibular feedback in favor of a direct feed-forward control of balance based on efference copies from the locomotor commands. Moreover, the phase-dependent modulation of vestibular influences would similarly reflect changes in the proportion of sensory vs. motor noise across the gait cycle. An analogous re-weighting of sensory vs. motor cues based on the relative precision of these signals could further explain the previously described speed- and phase-dependent modulation of other non-vestibular feedback cues (i.e., visual and proprioceptive) during human locomotion[45–49].

The relationship between the activity-dependent modulation of vestibular influences and changes in HMP suggests that during human locomotion an intrinsic feed-forward mechanism based on locomotor efference copies plays a significant part in balance regulation, which was previously thought to be predominantly governed by sensorimotor reflexes. Traditionally, motor efference copies are primarily considered to serve as predictors of sensory consequences arising from one's own actions, thereby enabling the brain to distinguish self-generated sensory signals (reafference) from sensory inputs caused by unpredictable external influences (exafference)[50–52]. Recent research, however, has expanded this view, suggesting that internal motor predictions are also involved in coordinating action of different motor systems that are otherwise functionally and anatomically unrelated[14]. One well described example of such an efference copy-mediated motor-to-motor coupling is the interaction between the mammalian locomotor and respiratory motor system, which is coordinated by intrinsic efference copies derived from CPG activity in the lumbar spinal cord[53]. More recently, CPG-derived locomotor efference copies were shown to directly mediate compensatory eye movements for gaze stabilization during aquatic locomotion in *Xenopus laevis* tadpoles[10] and adult frogs[15] – a task that is usually thought to be mediated by the vestibulo-ocular reflex. Importantly, the direct coupling between spinal and ocular motor signals was shown to be accompanied by a selective suppression of both ex- and reafferent vestibular inputs to extraocular motoneurons. Moreover, the

activity-dependent suppression was proven to be plane-specific and only interfered with vestibular inputs related to the primary plane of head movements during aquatic locomotion. Whether such a selective and plane-specific gating of total vestibular inflow occurs at the level of the brainstem extraocular or vestibular nuclei or other brain regions such as the cerebellum yet remains unknown. In favor of a cerebellar origin, it was previously shown that the phasic modulation of vestibulospinal neuron activity in the lateral vestibular nucleus observed during locomotion in cats depends on the presence of an intact cerebellum and is disrupted by its removal[54,55]. Given its prominent role in adaptive plasticity of vestibular reflexes[1,56,57], the cerebellum might thus serve as a convergence site for the weighting and integration of self-motion derived vestibular cues and intrinsic locomotor efference copies.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

All of the authors have taken part in the preparation of this manuscript, have reviewed the results, and have approved the final version of this manuscript. H.D., R.S., S.G. and M.W. conceptualized and designed the study. H.D., F.H., R.S., P.R.M., S.G. and M.W. collected, analyzed, and interpreted the data. H.D. and M.W. wrote the paper.

Competing interests

The authors declare no competing interest.

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6.2. Publication II: “Downbeat nystagmus becomes attenuated during walking compared to standing”

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ORIGINAL COMMUNICATION

Downbeat nystagmus becomes attenuated during walking compared to standing

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Abstract
Downbeat nystagmus (DBN) is a common form of acquired fixation nystagmus related to vestibulo-cerebellar impairments and associated with impaired vision and postural imbalance. DBN intensity becomes modulated by various factors such as gaze direction, head position, daytime, and resting conditions. Further evidence suggests that locomotion attenuates postural symptoms in DBN. Here, we examined whether walking might analogously influence ocular-motor deficits in DBN. Gaze stabilization mechanisms and nystagmus frequency were examined in 10 patients with DBN and 10 age-matched healthy controls with visual fixation during standing vs. walking on a motorized treadmill. Despite their central ocular-motor deficits, linear and angular gaze stabilization in the vertical plane were functional during walking in DBN patients and comparable to controls. Notably, nystagmus frequency in patients was considerably reduced during walking compared to standing ($p < 0.001$). The frequency of remaining nystagmus during walking was further modulated in a manner that depended on the specific phase of the gait cycle ($p = 0.015$). These attenuating effects on nystagmus intensity during walking suggest that ocular-motor control disturbances are selectively suppressed during locomotion in DBN. This suppression is potentially mediated by locomotor efference copies that have been shown to selectively govern gaze stabilization during stereotyped locomotion in animal models.

Keywords Downbeat nystagmus · Locomotion · Gaze stabilization · Motor efference copy

Introduction

Downbeat nystagmus (DBN), a frequent form of acquired fixation nystagmus, is characterized by a spontaneous upward drift of the eyes compensated by fast resetting saccades directed downwards. Patients suffer from visual disturbance due to vertical oscillopsia, to-and-fro vertigo, postural ataxia, and an increased risk of falling [10, 23, 24, 29]. DBN has been associated with impairments in central vestibulo-cerebellar areas [11, 13]. Several hypothetical pathomechanisms have been suggested in the past, such as (1) a central tone imbalance in pathways mediating the vertical vestibulo-ocular reflex (VOR) or smooth pursuit eye movements, or (2) a diminished inhibitory influence of vestibulo-cerebellar Purkinje cells on vertical ocular-motor pathways mediating gaze holding and smooth pursuit [19, 21]. However, the precise etiology of the disease remains hitherto unknown.

The intensity of DBN-related symptoms is known to be modulated by a variety of factors. Accordingly, nystagmus intensity depends on the direction of gaze, the orientation of the head relative to gravity, and illumination [8, 18, 25]. Ocular-motor symptoms typically attenuate during daytime and after prolonged upright resting [26, 27]. More recently it has been found that postural instability in DBN patients is modulated during locomotion: Whereas they exhibit a staggering, broad-based (sensory)-ataxic gait during slow walking, postural deficits diminish during faster walking modes [24]. This locomotion-dependent modulation has been hypothesized to result from a selective suppression of the destabilizing pathological vestibulo-cerebellar influence on balance during fast walking.

It is unknown whether and how locomotion might also affect ocular-motor symptoms in DBN. Symptoms could either improve in a manner analogous to postural stability or even be further aggravated due to the hypothesized central

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VOR deficits in DBN. Since visual disturbance during walking presents a major risk factor for falling [16], the present study systematically examines gaze stabilizing mechanisms during locomotion as well as walking-related influences on nystagmus intensity in patients with DBN.

Materials and methods

Participants

Ten patients with DBN (3 females; mean age 62.6 ± 12.5 years, mean height 172.4 ± 10.4 cm, and mean weight 80.2 ± 17.3 kg) participated in the study (Table 1). Patients underwent a complete neurological and physical examination including testing of sensory and postural dysfunction and an MRI scan of the brainstem and cerebellum. Seven patients had DBN due to an idiopathic etiology and 3 patients had secondary forms of DBN either due to sporadic adult-onset cerebellar atrophy ($N = 2$) or episodic ataxia type 2 ($N = 1$). Ten healthy, age-matched subjects (3 females; mean age 62.8 ± 5.7 years, mean height 173.2 ± 10.8 cm, and mean weight 71.9 ± 7.0 kg) without any auditory, vestibular, neurologic, cardio-vascular or orthopedic disorders served as controls. All participants had normal or corrected-to-normal vision.

Experimental procedure

Horizontal and vertical eye movements during standing and walking were captured at a sampling rate of 220 Hz using a monocular head-mounted video-oculography system (EyeSeeTec GmbH, Munich, Germany) as described previously [7]. The monocular camera was attached to light-weight goggles, tightly strapped around the subject's head to prevent slippage. An inertial measurement unit integrated in the center of the camera was used to record 6D head motion (angular and linear). During all recordings, subjects fixated on a red point (visual angle of ~ 0.35°) at a distance of 2.0 m straight ahead of them at standing eye level. For the locomotion experiments, participants walked at their own pace and preferred speed for two minutes on a pressure-sensitive treadmill (Zebris®, Isny, Germany; h/p/cosmos®, Nussdorf-Traunstein, Germany). DBN patients were secured with a safety belt. Subjects were asked to visually fixate on the red point at all times and to minimize eye blinks during recordings. Recordings during standing and walking were performed in randomized order to control for potential habituation effects.

Gait analysis

Walking performance of each participant was estimated by calculating the following gait cycle parameters: gait velocity, the mean and the coefficient of variation (CV) of stride length, stride time, base of support as well as the percentage of double support and swing phases with respect to the total gait cycle duration.

Processing of raw eye movement data

Eye movement recordings were initially screened for potential motion artifacts [7]. Eye blinks during the recordings were identified using a Kalman filter and resulting gaps shorter than 10 ms were closed using cubic spline interpolation in the eye position trace [20]. Larger gaps were excluded from further analysis. Linear head acceleration

Table 1 Clinical and nystagmus characteristics of patients

No	Age (y)	Sex	Additional neuro-ophthalmological findings	MRI findings	Etiology	Medication	Time since diagnosis (y)	DBN frequency (Hz)	
								Standing	Walking
1	60	f	1, 2, 3	–	Idiopathic	Fampridine 10 mg 1-0-1	5	2.6	2.3
2	40	m	1, 2, 3, 5	2, 4	Idiopathic	Fampridine 10 mg 1-0-1	12	1.6	0.4
3	58	m	2, 3, 4	1	Idiopathic	Gabapentin 600 mg 1-0-1	2	3.0	2.3
4	45	m	1, 2, 3, 4, 5, 6	–	EA2	4-Aminopyridine 5 mg 1-1-1-1	6	1.8	0.6
5	73	m	1, 2, 3, 4, 6,	1	Idiopathic	Fampridine 10 mg 1-0-1	5	2.2	1.6
6	71	m	1, 2, 3, 5	–	Idiopathic	4-Aminopyridine 5 mg 1-1-1-1	2	2.2	0.9
7	80	m	1, 2, 3, 4, 5	–	Idiopathic	Fampridine 10 mg 1-0-0	2	1.5	1.2
8	71	f	2, 3, 4	2	SAOA	Fampridine 10 mg 1-0-0	2	2.6	1.8
9	63	f	1, 2, 3, 5	2	SAOA	Fampridine 10 mg 1-0-0	1	2.1	0.9
10	65	m	2, 3, 4	–	Idiopathic	Fampridine 10 mg 1-0-0	3	1.1	0.4

Additional neuro-ophthalmological findings: 1: gaze-evoked nystagmus, 2: saccadic smooth pursuit, 3: impaired visual fixation suppression of the vestibulo-ocular reflex, 4: head shaking nystagmus, 5: pathological head impulse test, 6: rebound nystagmus; MRI findings: 1: midline cerebellar atrophy, 2 pancerebellar atrophy, 3 cerebellar neoplasm, 4 cerebellar vascular lesion, 5 cerebellar post-inflammatory lesion; etiology: SAOA: sporadic adult-onset ataxia, EA2: episodic ataxia type 2

was integrated to obtain linear head velocity and position. To quantify the impact of linear head motion on image slip, the angular shift of the target that would have been created by the linear motion was calculated using trigonometric functions (see [7] for details). Locomotion recordings were segmented into gait cycles defined by the time points of successive left foot heel contact based on the ground reaction force profiles obtained from the pressure-sensitive treadmill.

VOR analysis

For the VOR gain calculation, eye velocity was low-pass filtered using a fourth-order Butterworth filter with a cutoff frequency of 10 Hz to remove fast phase eye movements, such as during nystagmus. Angular head velocity and linear head acceleration were filtered analogously. For each locomotion trial, the eye velocity and head angular/linear velocity traces were segmented for successive gait cycles and resampled to the average gait cycle duration of the recording. To quantify VOR responses during walking, the angular and linear VOR gain (slopes of least squares regression of eye *vs* head velocity; see [7]) were calculated for each gait cycle separately and subsequently averaged across all gait cycles.

DBN frequency analysis

DBN intensity is usually quantified as the mean velocity of the slow upward drift of the eyes (i.e., slow phase velocity). Since during locomotion the DBN-related slow phase eye motions are superimposed by slow, VOR-driven eye movements, it is impossible to determine the exact slow phase velocity of DBN during walking. Thus, to quantify the intensity of DBN symptoms during locomotion, we focused on the mean frequency of DBN quick phases (i.e., the downward-directed resetting saccades) [30]. As a first step, vertical eye velocity was band-pass filtered using a fourth-order Butterworth filter (between 10 and 30 Hz) to remove any low-frequency eye movements (slow VOR responses and DBN-related upward drift) that occur during walking. Fast downward saccades were then identified as DBN quick phases unless they coincided with fast angular (aVOR) or linear (lVOR) VOR responses that occur e.g. during fast head movements after heel strike. These VOR responses were specified as downward eye movements occurring at the same time and with approximately the same magnitude as oppositely directed (upward) head movements. DBN frequency was first quantified as the average frequency of complete standing and walking trials. DBN frequency was further analyzed in relation to the phase of the gait cycle. For the latter, time points of DBN-related quick phases were identified during each gait cycle and normalized to the mean gait cycle duration. DBN frequency was then calculated for 100 equally long time windows throughout the gait cycle. Based on this analysis, the average phase-dependent DBN frequency was computed for each walking trial and a time–frequency density plot of DBN occurrence across the gait cycle was generated from the pooled data of all walking trials of patients (see Fig. 3).

Statistical analysis

Descriptive statistics are reported as mean ± standard deviation (SD). Differences in gait performance, VOR gains, and nystagmus frequency were analyzed using Student's independent two-sample *t*-test. Activity-dependent differences of nystagmus frequency in patients were analyzed using Student's paired two-sample t-test. Statistical analysis was performed using IBM SPSS (Version 26.0, IBM Corp., Armonk, NY, USA). Results were considered significant at $p < 0.05$.

Results

Gait alterations in patients with DBN

Patients and controls showed comparable self-chosen speeds (0.8 ± 0.24 m/s vs. 0.84 ± 0.18 m/s) and step frequencies (107.4 ± 18.8 steps/min vs. 99.0 ± 14.1 steps/min) while walking on the treadmill. Patients exhibited walking alterations typically observed in (sensory)-ataxic gait disorders, with an increased base of support (0.17 ± 0.06 m vs. 0.10 ± 0.03 m, $p = 0.041$) and increased spatiotemporal gait variability (stride length CV: 5.3 ± 2.9% vs. 2.2 ± 0.7%, $p = 0.005$; stride time CV: 4.0 ± 2.6% vs. 1.7 ± 0.6%, $p = 0.014$). Other spatiotemporal gait characteristics were comparable between patients and controls (stride length: 0.89 ± 0.23 m vs. 1.03 ± 0.13 m; stride time: 1.15 ± 0.23 s vs. 1.26 ± 0.19 s, base of support CV: 13.4 ± 8.9% vs. 16.9 ± 6.8%, swing phase: 33.9 ± 2.8% vs. 36.0 ± 2.3%; double support phase: 32.1 ± 5.7% vs. 28.5 ± 4.0%).

Normal gaze stabilization reflexes during walking in patients with DBN

Eye movements need to counteract angular and linear head motion during walking to prevent image slip, especially in the vertical plane. Both vertical eye and angular head movements were comparable between patients and healthy controls (Fig. 1A). Gaze stabilization mechanisms in the angular and linear vertical plane, quantified by the gain of the vertical angular and linear VOR (i.e., aVOR and lVOR), were found to be comparable between patients and healthy controls (Fig. 1B, C). Hence, despite of a continuous nystagmus, eye movements in patients with DBN that are driven by gaze stabilizing reflexes, appear to remain functional.

DBN frequency decreases during walking

During standing while fixating on a red point straight in front of the head, all patients displayed a continuous upward drift of the eye, compensated by regular downward quick phases (Fig. 2A). DBN frequency ranged between 1.1 and 3.0 Hz (average 2.1 ± 0.6 Hz) (see Table 1, Fig. 2B) in accordance with previous studies [14]. During walking at preferred speed and pace, DBN frequency decreased in all patients to an average value of 1.2 ± 0.7 Hz ($p < 0.001$) (Fig. 2B). In healthy controls, eye movements during walking solely resulted from normal gaze stabilizing mechanisms (i.e., aVOR and lVOR) to compensate concurring head motion (Fig. 1C).

DBN frequency depends on gait cycle phase

The frequency of DBN was not only affected by walking per se but was further found to be modulated during walking in a manner that depended on the phase of the gait cycle. Time–frequency analysis of nystagmus occurrence across the gait cycle revealed that DBN was more likely to occur during the single support phase (SSP) compared to the double support phase (DSP) of the gait cycle (Fig. 3A–C) ($p = 0.015$). This phase-dependent modulation of DBN frequency resulted in frequency peaks across the gait cycle that closely matched the timing of vertical aVOR gain peaks (see Fig. 3C, D).

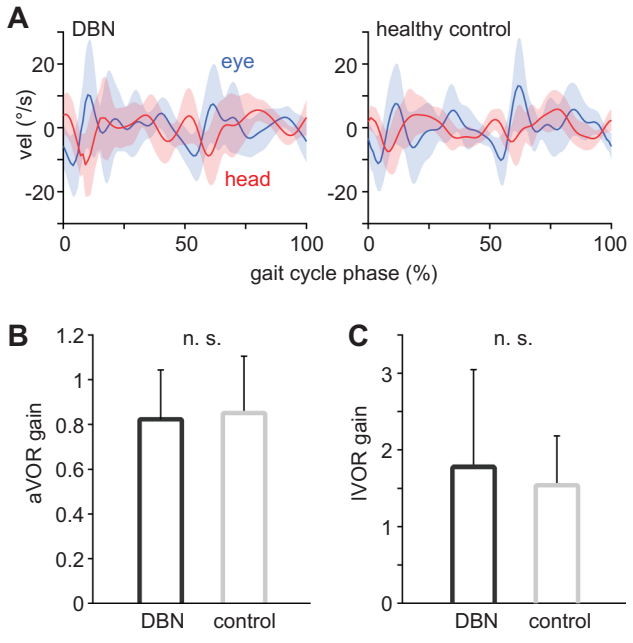

Fig. 1 Angular and linear VOR in patients and healthy controls. **A** Mean ± SD vertical angular head (red) vs. eye (black) movements throughout the gait cycle in patients with downbeat nystagmus (DBN; left) and healthy controls (right). **B**, **C** Linear and angular gaze stabilization, i.e., the gain of the angular (aVOR) and linear (lVOR) vestibulo-ocular reflex were comparable between patients and healthy controls

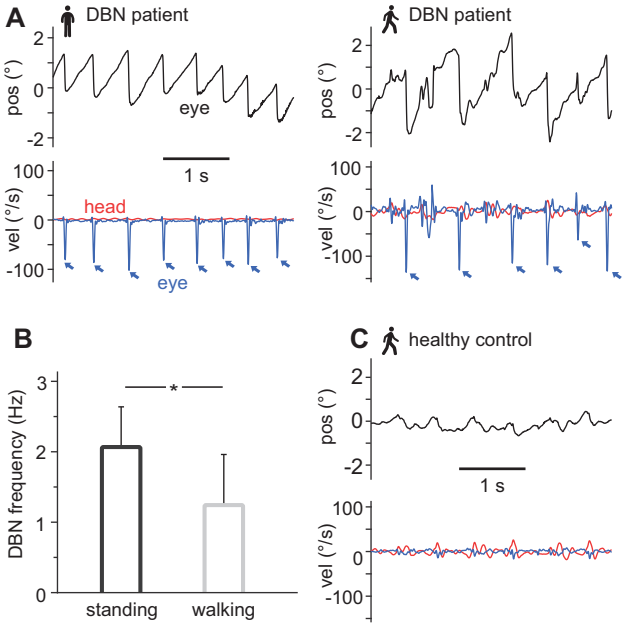

Fig. 2 Downbeat nystagmus frequency is reduced during walking. **A** Representative example of eye position (black), eye velocity (blue), and head velocity (red) during standing (left) and walking at preferred speed (right) in a patient with downbeat nystagmus (DBN). Blue arrows indicate occurrence of nystagmus quick phases. **B** Average DBN frequency during standing and walking at preferred speed. **C** Representative example of eye position/velocity and angular head velocity during walking at preferred speed in an age-matched healthy control. * indicates a significant difference

Discussion

Here we studied the impact of locomotion on general gaze stabilizing mechanisms and nystagmus characteristics in patients with DBN. During walking at preferred pace and velocity, patients exhibited a broad-based, staggering stepping pattern compatible with a sensory and/or cerebellar gait disorder [24]. In contrast to postural deficits, their vertical angular and linear gaze stabilization during walking turned out to be fully functional and comparable to that of healthy controls. This agrees with the previous observation of normal and symmetric VOR responses in response to passive head impulses in patients with DBN [9] and contradicts the hypothesis of a central tone imbalance in VOR pathways underlying ocular-motor symptoms in DBN [18, 21].

Spontaneous, downwards directed fixation nystagmus is the primary source for visual disturbance and oscillopsia in DBN. Nystagmus intensity is known to be influenced by

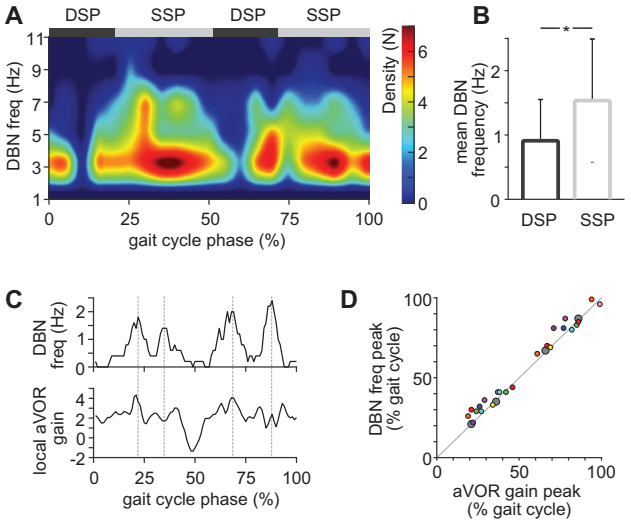

Fig. 3 Downbeat nystagmus frequency depends on the gait cycle phase. **A** Density plot of nystagmus occurrence during the gait cycle from the pooled walking trials of all patients. Downbeat nystagmus (DBN) frequency is modulated across the gait cycle and most prevalent during the single support phase (SSP) and the end of the double support phase (DSP). **B** Average differences in DBN frequency between DSP and SSP. **C** Exemplary phase-dependent modulation of DBN frequency (above) and parallel modulation of vertical angular vestibulo-ocular reflex (aVOR) gain across the gait cycle. **D** Peaks of phase-dependent DBN frequency vs. peaks of phase-dependent aVOR gain for all patients closely correspond (large grey dots represent patient data displayed in **C**). * indicates a significant difference

static changes in head position relative to gravity [18, 26]. So far it was unknown whether and how DBN might be also influenced by dynamic changes in head orientation such as they occur during locomotion. We observed that walking at preferred pace and speed resulted in a considerable reduction of nystagmus frequency, consistently in all examined patients irrespective of DBN etiology. This attenuation could result from activity-induced changes in head orientation and resultant alterations of vestibular input. DBN has been related to an overacting otolith-ocular reflex [3, 18] according to which the gravity-dependence of DBN should primarily reflect changes in otolithic input [18, 26]. However, due to fixation on a visual target at eye level during walking in our experiment, head orientation of patients was rather kept straight ahead. Moreover, walking has been generally associated with a slight downward tilt of the head in pitch plane [22], which should result in enhancement rather than attenuation of DBN according to the aforementioned assumption [18].

Alternatively, walking-induced attenuation of DBN symptoms could directly arise from locomotor-activity itself. In a previous study we could demonstrate that postural imbalance in DBN becomes attenuated during locomotion in particular during fast stereotyped walking [24]. Analogously, peripheral vestibular ocular-motor impairments such as spontaneous nystagmus in unilateral or deficient VOR in bilateral vestibulopathy are known to improve during locomotion [1, 12]. These observations have been collectively interpreted to reflect a selective central and/or peripheral suppression of sensory feedback during locomotion. A physiological substrate and mechanism for this activity-dependent suppression of sensory feedback has been revealed in amphibian animal models [15, 28]. In these animals, efference copies of the spinal locomotor command are conveyed to upper brain regions where they selectively suppress afferent vestibular input and directly supplement visuo-vestibular reflexes to ensure gaze stability during locomotion. Also in humans, theoretical approaches [4, 17], clinical observations [2, 12], and experimental evidence [5, 6] suggest the presence of an analogous predictive feed-forward regulation of gaze and postural stability during locomotion. Hence, efference copies of the locomotor command could likewise cancel out the destabilizing vestibulo-cerebellar drive that has been suggested to induce central ocular-motor and postural impairments in DBN patients.

A detailed investigation of the timing of remaining nystagmus occurrence during walking further demonstrated that the degree of DBN attenuation during locomotion depends on the specific gait cycle phase. These phasic changes in nystagmus intensity across the gait cycle parallel the phasic modulation of the VOR (Fig. 3C) and vestibulospinal reflexes during human locomotion [5, 6]. Hence, gait cycle phases where DBN is suppressed coincide with those where vertical VOR and vestibulospinal responses are selectively canceled out or attenuated. This observation further suggests that the attenuation of DBN while walking and the suppression of sensorimotor gaze and balance reflexes during locomotion share the abovementioned common mechanism.

In conclusion, the present findings demonstrate that while DBN has profound effects on patients walking ability, it does not impair general gaze stabilizing mechanisms during locomotion. However, walking in turn has an attenuating effect on nystagmus intensity in DBN. This observation parallels previous reports of a locomotion-induced mitigation of sensory ocular-motor and balance deficits during walking. We propose that a common mechanism based on a predictive feed-forward regulation of posture and gaze might explain this attenuation of peripheral and central sensorimotor balance and ocular-motor deficits. Subsequent studies should examine whether, in analogy to postural stability, walking-related attenuation of DBN becomes even more pronounced at non-preferred, fast walking modes. Besides, further investigations are required to explore the functional consequences of the present findings in particular related to the dynamic visual acuity and risk of falling in patients with DBN.

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Declarations

Conflicts of interest The authors report no competing interests.

Ethical standards The Ethics Committee of the Medical Faculty of the University of Munich approved the study protocol, which was conducted in conformity with the Declaration of Helsinki and participants gave their written informed consent.

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7. Summary

The aim of this thesis was to examine a possible explanation for the activity-dependent variability of the impact of vestibular feedback cues on balance and gaze regulation that was previously repeatedly observed in healthy and clinical populations.

In particular, we tested whether this modulation can be explained by the presence of a feed-forward mechanism regulating balance and gaze during human locomotion that was previously described in animals during aquatic locomotion.

To test this hypothesis, we built on a theoretical model (MacNeilage and Glasauer 2017) that makes verifiable hypothesis based on the presumed presence of a feed-forward regulation of balance (Dietrich, Heidger *et al.* 2020) and gaze control during self-motion. According to the model, there should be an inverse relationship between the relative weight of vestibular cues on balance and gaze control and the stereotype of head movements during locomotion.

In the first study, we experimentally determined in healthy individuals the gain of vestibulospinal reflexes by means of a galvanic vestibular stimulation while standing and walking at different speeds.

We could demonstrate that vestibular balance control becomes considerably suppressed (1) during walking compared to standing, (2) during fast compared to slow walking and (3) during specific periods of the gait cycle. In a next step, we could show that these modulations closely match concomitant experimentally quantified changes in head motion stereotype and are thus compatible with the model predictions.

Therefore, the results of this study deliver an explanation for the activity-dependent gating of sensory contribution to motor control and further support the concept of a locomotor efference copy based feedforward regulation of balance during human locomotion (Dietrich, Heidger *et al.* 2020).

In the second study, we evaluated the model predictions in a clinical population of patients with downbeat nystagmus. Postural symptoms in patients with downbeat nystagmus have been previously shown to be alleviated at faster locomotion, analogous to patients with afferent vestibular deficits (Schniepp, Wuehr *et al.* 2014). It was yet unknown, whether ocular-motor deficits in downbeat nystagmus, in particular the central nystagmus also become modulated during locomotion.

We therefore experimentally quantified compensatory eye movements driven by the vestibulo-ocular reflex and nystagmus intensity in patients with downbeat nystagmus during quiet standing compared to walking.

We could demonstrate that nystagmus in downbeat nystagmus becomes considerably suppressed (1) during walking compared to standing and (2) during specific periods of the gait cycle (Dietrich, Pradhan *et al.* 2022).

The pattern of these modulations closely matches the models predictions based on the assumption of the presence of a feedforward mechanism regulating gaze control during locomotion (MacNeilage and Glasauer 2017, Dietrich and Wuehr, 2019). These findings further suggest that the locomotion-dependent attenuation of downbeat nystagmus and the selective suppression of sensory input as observed during human locomotion are based on a common neuronal mechanism.

In conclusion, the two studies of this thesis provide evidence for the presence of an internal feed-forward mechanism regulating balance and gaze control during human locomotion that is based on predictive efference copies of the spinal locomotor command and supplements or even suppresses incoming vestibular feedback (Dietrich, Heidger *et al.* 2020).

The neuronal substrates of this mechanism in humans as well as the anatomical site where predictive feedforward and sensory feedback cues interact are as of yet unknown and demand for further investigation.

Furthermore, it could be worthwhile to evaluate whether specific rehabilitation programs may be suited to promote internal feedforward control of balance and gaze regulation and could thus be therapeutically used to improve balance and gaze stabilization deficits in patients with peripheral and/or central vestibular deficits.

8. Zusammenfassung

Ziel der vorliegenden Dissertation war es, eine Erklärung für die aktivitätsabhängige Modulation vestibulärer Einflüsse auf die Gleichgewichts- und Blickregulation zu untersuchen, die zuvor wiederholt bei Gesunden und Patienten mit sensorischen Erkrankungen beobachtet wurde.
Basierend auf vorausgegangenen Beobachtungen im Tiermodell während der aquatischen Lokomotion von Kaulquappen, wurde in dieser Arbeit insbesondere untersucht, ob diese Modulationen durch das gleichzeitige Auftreten einer Vorwärtskopplung der Gleichgewichts- und Blickregulation erklärbar sind.
Um diese Hypothese zu testen wurde ein theoretisches Modell genutzt (MacNeilage and Glasauer 2017), welches verifizierbare Aussagen über das Vorhandensein einer Vorwärtskopplung der Gleichgewichts- und Blickregulation während der Lokomotion trifft. Dem Modell zufolge sollte eine inverse Beziehung zwischen der relativen Gewichtung vestibulärer Einflüsse auf die Gleichgewichts- und Blickregulation und der Stereotypie von Kopfbewegungen während der Lokomotion bestehen.

In der ersten Studie wurde an gesunden Probanden experimentell der Wirkungsgrad vestibulospinaler Reflexe mit Hilfe einer galvanischen vestibulären Stimulation während des Stehens und Gehens mit unterschiedlichen Geschwindigkeiten bestimmt.
Dabei konnte gezeigt werden, dass vestibuläre Haltungsreflexe selektiv unterdrückt werden (1) beim Gehen im Vergleich zum Stehen, (2) beim schnellen im Vergleich zum langsamen Gehen und (3) während bestimmter Perioden des Gangzyklus. In einem nächsten Schritt konnten gezeigt werden, dass die Modulation vestibulärer Reflexe eng zusammenhängt mit experimentell quantifizierbaren Veränderungen in Regelmäßigkeit der Kopfbewegungen während des Gehens.
Die Ergebnisse dieser Studie liefern somit eine plausible Erklärung für die dynamische Gewichtung vestibulärer Einflüsse zwischen und innerhalb verschiedener Aktivitäten und stützen die Annahme einer vorwärtsgekoppelten Gleichgewichtsregulation während der menschlichen Lokomotion welche auf Efferenzkopien motorischer Lokomotionsbefehle aus dem Rückenmark basiert (Dietrich, Heidger *et al.* 2020).

In der zweiten Studie wurden die Vorhersagen des Modells in einer klinischen Population von Patienten mit Downbeat-Nystagmus evaluiert. In einer vorangegangenen Studie konnte gezeigt werden, dass posturale Symptome bei Patienten mit Downbeat-Nystagmus während schneller Lokomotion abnehmen, analog zu Patienten mit peripheren vestibulären Defiziten (Schniepp, Wuehr *et al.* 2014). Es war bisher unbekannt, ob die okulomotorische Störung beim Downbeat-Nystagmus, insbesondere der zentrale Nystagmus, ebenfalls durch die Lokomotion moduliert werden.

Um diese Frage zu klären, wurden die Blickstabilisierungsmechanismen und die Nystagmusintensität von Patienten mit Downbeat-Nystagmus beim Gehen im Vergleich zum ruhigen Stehen experimentell quantifiziert.
Dabei konnte gezeigt werden, dass der Nystagmus selektiv unterdrückt wird (1) während des Gehens im Vergleich zum Stehen und (2) während bestimmter Perioden des Gangzyklus (Dietrich, Pradhan *et al.* 2022).
Das Muster dieser Nystagmus-Modulationen stimmt gut mit den Vorhersagen des Modells überein, welche auf der Annahme einer Vorwärtskopplung der Blickstabilisierung während der menschlichen Lokomotion basieren. Diese Beobachtungen deuten darauf hin, dass der lokomotionsabhängigen Unterdrückung des Downbeat-Nystagmus und der selektiven Unterdrückung sensorischen Inputs während der Lokomotion ein gemeinsamer Mechanismus zu Grunde liegt.

Zusammenfassend konnten die beiden Studien der vorliegenden Dissertation Hinweise für das Vorhandensein einer internen Vorwärtskopplungskontrolle der Blick- und Haltungskontrolle während der menschlichen Lokomotion liefern. Aus vorangegangenen Tierstudien lässt sich vermuten, dass diese Vorwärtskopplungskontrolle auf Efferenzkopien der motorischen Lokomotionsbefehle aus dem Rückenmark basiert, die eingehende vestibuläre Rückkopplungssignale ergänzen oder sogar unterdrücken. Ein entsprechendes neuronales Substrat dieses Mechanismus beim Menschen sowie die anatomische Schaltstelle, an der die prädiktiven Vorwärtskopplungs- und sensorischen Rückkopplungssignale interagieren sind noch unbekannt und bedürfen weiterer Untersuchungen.
Des Weiteren könnte es lohnend sein zu untersuchen, ob sich spezifische Rehabilitationsprogramme eignen, die interne Vorwärtskopplungskontrolle zu trainieren und somit einen therapeutischen Ansatz liefern, um Defizite der Blick- und Haltungskontrolle bei Patienten mit peripheren und/oder zentralen vestibulären Defiziten zu verbessern.

9. Statement of research contribution

The scientific topic of the present doctoral thesis “Activity-dependent modulation of human balance and gaze control” was defined in close dialogue with my supervisors Roman Schniepp and Max Wühr. Together we formulated the research questions, conceptualized and designed the two studies.

I was responsible for the recruitment of study participants (patients and healthy study subjects) in both studies with assistance by Haike Dietrich. With support by Haike Dietrich and Max Wühr, I conducted the data collection which included instruction of study participants, preparation and calibration of stimulators and recording devices and eventually the recording of participants.

The preliminary analysis and interpretation of the data from both publications was done by myself in close dialogue with Max Wühr and Haike Dietrich. I wrote the draft of the first manuscript of “Head motion predictability explains activity-dependent suppression of vestibular balance control” with assistance by Haike Dietrich. Therefore, the authorship of the first publication is a shared firstauthorship between Haike Dietrich and me.

The draft of the second manuscript "Downbeat nystagmus becomes attenuation walking compared to standing" was primarily prepared by Haike Dietrich and Max Wühr.

I contributed to the reviewing process of both publications by applying the desired changes to the manuscripts according to the reviewers’ wishes in close cooperation with all co-authors.

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