Einfluss einer galvanischen vestibulären Rauschstimulation auf die Gangstabilität bei gesunden Probanden und bei Patienten mit bilateraler Vestibulopathie

Eva Nusser

2021

Aus der Neurologischen Klinik und Poliklinik
Vorstand: Prof. Dr. Marianne Dieterich

und

dem Deutschen Schwindel- und Gleichgewichtszentrum – IFB
Vorstand: Prof. Dr. Dr. Thomas Brandt

Kliniken der Ludwig-Maximilians-Universität München

Einfluss einer galvanischen vestibulären Rauschstimulation auf die Gangstabilität bei gesunden Probanden und bei Patienten mit bilateraler Vestibulopathie

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der Ludwig-Maximilians-Universität zu München

vorgelegt von

Eva Nusser

aus

München

2021

Mit Genehmigung der Medizinischen Fakultät
der Ludwigs - Maximilians - Universität München

Berichterstatter:	Prof. Dr. Klaus Jahn
Mitberichterstatter:	PD Dr. Katharina Feil PD Dr. Viktor Arbusow
Mitbetreuung durch den promovierten Mitarbeiter:	Dr. Max Wühr
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	04.03.2021

Eidesstattliche Erklärung

Ich versichere hiermit an Eides statt, dass die vorgelegte Dissertation von mir selbständig und ohne unerlaubte Hilfe angefertigt worden ist. Des Weiteren erkläre ich, dass die Dissertation nicht ganz oder in wesentlichen Teilen einer anderen Prüfungskommission vorgelegt worden ist und dass ich mich nicht anderweitig einer Doktorprüfung ohne Erfolg unterzogen habe.

München, den 16.03.2020

Eva Nusser

Inhaltsverzeichnis

1. Einleitung

Für die Aufrechterhaltung der dynamischen Haltungsstabilität während des Gehens bedarf es einer kontinuierlichen sensorischen Kontrolle durch die visuellen, vestibulären und somatosensorischen Sinnesorgane.
Bei Beeinträchtigung oder Verlust der sensorischen Rückkopplungskontrolle kommt es während des Gehens zu verstärkten Fluktuationen in den Bewegungsabläufen verbunden mit einer verringerten Gangstabilität und einer erhöhten Sturzgefahr (Gandevia, McCloskey et al. 1992) (Nashner 1980).

Vorangegangene Studien haben gezeigt, dass durch eine unterschwellige stochastische Stimulation sensorischer Systeme die Reizschwelle des Systems herabgesetzt und damit die Informationsverarbeitung im System verbessert werden kann. Dieses Phänomen wurde bereits für das visuelle, auditive, somatosensorische und vestibuläre System nachgewiesen. Der zugrundeliegende Mechanismus, der die Verstärkung schwacher Eingangssignale durch die Interaktion mit einer unspezifischen stochastischen Rauschaktivität beschreibt, ist bekannt als „stochastische Resonanz“ (Moss, Ward et al. 2004).

Das Prinzip der stochastischen Resonanz wurde in vorangegangenen Studien bereits erfolgreich therapeutisch genutzt. So konnte gezeigt werden, dass eine Verstärkung der sensorischen Rückkopplung durch eine schwache somatosensorische (vibrierende Schuhsohlen) oder vestibuläre (rauschhafte galvanische vestibuläre Stimulation) Reizung zu einer effektiven Stabilisierung des Haltungsgleichgewichts von Patienten mit somatosensorischen und vestibulären Defiziten führt (Priplata, Niemi et al. 2003) (Iwasaki, Yamamoto et al. 2014) (Mulavara, Fiedler et al. 2011).

Aufbauend auf den bisherigen Studien zum therapeutischen Nutzen stochastischer Resonanz ist das Ziel der hier vorgestellten Arbeiten, den Einfluss einer unterschwelligen vestibulären Rauschstimulation auf das subjektive Balanceempfinden und auf die objektive Haltungsstabilität während des Gehens bei gesunden Probanden und bei Patienten mit einem beidseitigen Vestibularisausfall zu untersuchen.

2. Vestibuläre Haltungs- und Gangregulation

Das vestibuläre System vermittelt Informationen über Lage und Beschleunigung des Kopfes im Raum. Der Aufbau in Sacculus und Utriculus (Otolithenorgane) sowie in die Ductus semicirculares (Bogengänge) ermöglicht es sowohl lineare Beschleunigungen als auch Drehbeschleunigungen wahrzunehmen (Gray 1955).

Die in etwa im rechten Winkel zueinander positionierten Otolithenorgane enthalten die Maculae, besetzt mit Sterozilien, welche in eine gallertartige Membran einstrahlen. Diese Membran trägt an ihrer Oberfläche einen dichten Besatz von Kalziumkarbonatkristallen (Otolithen). Ein Reiz für die Sinneszellen entsteht dadurch, dass bei linearer Beschleunigung die trägen Otholithen durch die Fliehkraft zu einer scherkraftartigen Verschiebung der Otholithenmembran führen. Die daraus resultierende Ablenkung der Sterozilien hat eine Erregung der Sinneszellen zur Folge.
In den drei in etwa senkrecht zueinander orientierten Bogengängen kommt es ebenso zu einer Erregung durch das Ablenken der Sterozilien. Diese ragen hier in die gallertartige Cupula hinein, welche von Endolymphe umgeben ist. Die Endolymphe wird durch Drehbewegungen beschleunigt und lenkt somit die Cupula aus.
Durch die Auslenkung der Stereozilien kommt es zu einem Einstrom des endolympahtischen Kaliums, was eine Depolarisation der Zelle mit nachfolgendem Calciumeinstrom bewirkt. Der Anstieg des intrazellulären Calciums führt zu einer vermehrten Transmitterfreisetzung in den synaptischen Spalt mit anschließender Stimulation der afferenten Nervenfasern, der sogenannten mechanoelektrischen Transduktion (Trepel 1999).
Die Informationen gelangen über den Gleichgewichtsnerven (N. vestibularis) zu den Gleichgewichtskernen (Ncll. vestibulares) im Hirnstamm. Diese erhalten zusätzliche Projektionen aus dem Rückenmark und dem Kleinhirn. Die wichtigsten Efferenzen der Vestibulariskerne ziehen zum Thalamus, in das Kleinhirn, zu den Augenmuskelkernen und in das Rückenmark (Horak, Shupert et al. 1994) (Trepel 1999).
Neben der Wahrnehmung von Position und Bewegung des Kopfes im Raum, vermitteln vestibuläre Afferenzen der Otolithenorgane und Bogengänge zwei wesentliche Reflexfunktionen für die Stabilisierung des Blicks während dynamischer Kopfbewegungen (vestibulookulärer Reflex) und die gleichzeitige Regulation des Haltungsgleichgewichts

(vestibulospinaler Reflex). Der vestibulookuläre Reflex zählt zu den Hirnstammreflexen. Er ermöglicht eine dynamische Blickstabilisierung, wobei die bei Kopfbewegung resultierende retinale Bildverschiebung durch entgegen gerichtete Augenbewegungen kompensiert wird. Vestibulospinale Haltungsreflexe bringen den Körper, ausgelöst durch vestibuläre Reize (z.B. Fallen, Wegrutschen eines Beins beim Nachgeben der Unterlage), durch Streckbewegungen (Aktivierung von Strecker-Motoneuronen, Hemmung der Beuger-Motoneuronen) unbewusst wieder ins Gleichgewicht (Trepel 1999).

3. Bilaterale Vestibulopathie

3.1. Ätiologie, Symptomatik und Therapieansätze

Der beidseitige Ausfall der Gleichgewichtsfunktion, die bilaterale Vestibulopathie (BVP), ist die häufigste Ursache eines bewegungsabhängigen Schwankschwindels. In einer spezialisierten Schwindelambulanz machte die bilaterale Vestibulopathie 7,3 % aller vorstelligen Schwindelsyndrome aus (Brandt 2012). Die häufigsten Ursachen einer BVP sind: Einnahme ototoxischer Antibiotika (13%), bilateraler Morbus Meniere, entzündliche Erkrankungen (Meningitis, Enzephalitis, Zerebellitis), Autoimmunerkrankungen, zerebelläre Degenerationen und Tumore (z.B. beidseitiges Vestibularisschwannom bei Neurofibromatose Typ 2). Bei 50% der Patienten bleibt trotz umfangreicher neurootologischer Testung die Ätiologie unklar (idiopathische BVP) (Zingler, Weintz et al. 2008). Klinisch äußert sich die BVP in einem bewegungsabhängigen Schwankschwindel mit Gangunsicherheit, in einer Störung der dynamischen Blickstabilisierung (Oszillopsien mit Scheinbewegungen der Umwelt) sowie des Raumgedächtnisses und der Navigationsfunktion (Brandt, Schautzer et al. 2005).

Obwohl die überwiegende Anzahl der Patienten mit BVP eine vestibuläre Restfunktion behält, ist die Langzeitprognose der Erkrankung schlecht. Etwa 80% der Patienten zeigten keine wesentliche Verbesserung der Symptomatik in Follow-up-Untersuchungen. Die einzig bislang etablierte Therapieoption für Patienten mit BVP besteht in einer physikalischen Therapie mit Training der Gleichgewichts-, Gang- und Blickstabilisierungsfunktion. Studien zum Einsatz einer physikalischen Therapie bei Patienten mit BVP konnten eine teilweise Wiederherstellung der Gang- und Blickstabilisierungsfunktion nachweisen (Krebs, Gill-Body

et al. 1993) (Herdman, Hall et al. 2007). Jedoch stellt sich nur bei etwa der Hälfte der Patienten eine signifikante Funktionsbesserung in Folge der Therapie ein. Die Behandlungseffekte eines physikalischen Trainings fallen meist moderat aus (Gillespie and Minor 1999). Aus diesen Gründen wurde in den letzten Jahren als alternativer Therapieansatz die Entwicklung einer Prothese für das Gleichgewichtsorgan vorangetrieben. Ziel der Prothese ist es, durch eine gezielte Stimulation des Gleichgewichtsnerven die natürliche Gleichgewichtsfunktion nachzuahmen. Vielversprechende Ergebnisse zeigten sich in ersten Anwendungen mit Prototypen der Prothese im Tiermodell und bei einzelnen Patienten. Die mit der Implantation der Prothese verbundenen operativen Prozeduren sind jedoch hoch invasiv und bergen ein nicht geringes Risiko die Hörfunktion zu beschädigen.

3.2. Gangstörung

In Folge des beidseitigen Ausfalls der Gleichgewichtsfunktion kommt es bei Patienten mit BVP zu einer sensorisch-ataktischen Gangstörung mit deutlich erhöhtem Risiko zu stürzen. Das Gangbild ist gekennzeichnet durch einen breitbasigen Gang mit reduzierter Schrittlänge, erhöhter Rumpfabweichung, verlängerten Doppelstandphasen und insbesondere einer erhöhten spatiotemporalen Variabilität der Schritt-zu-Schritt-Folge (Gangvariabilität) (Wuehr, Schniepp et al. 2014). Die Ganggeschwindigkeit bei Patienten mit BVP ist meist nur moderat reduziert (Schniepp, Wuehr et al. 2012).

Die sensorisch-ataktische Gangstörung bei BVP ist typischerweise unterschiedlich ausgeprägt in Abhängigkeit von der Ganggeschwindigkeit. So äußert sich der sensorische Funktionsverlust mit Ganginstabilität und erhöhter Gangvariabilität vornehmlich während des langsamen Gehens. Mit zunehmender Ganggeschwindigkeit normalisiert sich die Symptomatik. Eine funktionierende vestibuläre Rückkopplungskontrolle ist somit vor allem wichtig für die Haltungsregulation während des langsamen Gehens, wohingegen schnellere Gangmodi hauptsächlich durch automatisierte Netzwerke im Rückenmark kontrolliert werden (Jahn, Strupp et al. 2000). Demensprechend konnten frühere Studien zeigen, dass der tonisch destabilisierende Einfluss eines einseitigen Vestibularisausfalls oder einer künstlichen vestibulären Reizung mit zunehmender Ganggeschwindigkeit abnimmt (Brandt, Strupp et al. 1999) (Jahn, Strupp et al. 2000). Eine korrespondierende Deaktivierung

sensorischer Kortexareale zeigte sich in funktionellen Bildgebungsstudien (Jahn, Deutschlander et al. 2004).

Der destabilisierende Einfluss des vestibulären Funktionsausfalls auf die Gangregulation kann normalerweise gut kompensiert werden durch die noch funktionierenden visuellen und somatosensorischen Sinnessysteme. Ein kompletter Verlust des Haltungsgleichgewichts entsteht typischerweise bei Patienten mit BVP erst, wenn die visuellen und somatosensorischen Rückmeldungen zusätzlich beeinträchtigt sind wie z. B. beim Gehen im Dunkeln oder auf unebenem Grund (Horak, Shupert et al. 1994).

4. Stochastische Resonanz zur Verbesserung der vestibulären Informationsverarbeitung

Üblicherweise geht man davon aus, dass Rauschen die Weiterleitung von Informationen und die Wahrnehmung von Signalen beeinträchtigt. Im Gegensatz dazu gibt es jedoch auch Hinweise, dass unter bestimmten Umständen das Vorhandensein eines schwachen Rauschsignals die Informationsverarbeitung verbessern kann. Dieses Phänomen ist als stochastische Resonanz bekannt. Die stochastische Resonanz tritt insbesondere in nicht-linearen Informationsverarbeitungssystemen auf, in denen Signale erst oberhalb eines bestimmten Schwellenpotentials weiterverarbeitet werden können. Demgemäß können schwache, unterschwellige Signale durch Interaktion mit einem zusätzlichen Rauschsignal so verstärkt werden, dass sie das Schwellenpotential erreichen und somit die Information weiterverarbeitet werden kann. (Moss, Ward et al. 2004).

Abbildung 1: Prinzip der Stochastischen Resonanz: Ein unterschwelliger Reiz (1) wird durch Interaktion mit einem schwachen Rauschsignal (2) über das Schwellenpotential verstärkt (3) und kann somit weiterverarbeitet werden.

In vorangegangenen Studien konnte gezeigt werden, dass das Phänomen der stochastischen Resonanz in der auditiven, taktilen und visuellen Wahrnehmung eine Rolle spielt. So lässt sich beispielsweise der menschliche Tastsinn durch Beigabe eines mechanischen oder elektrischen Rauschreizes auf der Hautoberfläche sensibilisieren. Des Weiteren führt ein schwaches Rauschsignal im Innenohr zu einer Herabsetzung der Wahrnehmungsschwelle für eingehende Tonsignale. Beide Phänomene wurden in der Vergangenheit bereits erfolgreich therapeutisch genutzt und finden Anwendung in neueren Generationen sensorischer Prothesen.

Das Phänomen der stochastischen Resonanz lässt sich auch in der vestibulären Informationsverarbeitung beobachten. Im Tierexperiment konnte gezeigt werden, dass sich die mechanoelektrische Transduktion der Haarzellen im Innenohr durch Beigabe eines schwachen mechanischen Rauschreizes optimieren lässt (Jaramillo and Wiesenfeld 1998). Auch im menschlichen Gleichgewichtsorgan lässt sich die stochastische Resonanz mit Hilfe einer schwachen, rauschhaften galvanischen vestibulären Reizung (GVS) auslösen. GVS ist eine einfache und sichere Methode, die es erlaubt die Aktivität vestibulärer Afferenzen über eine von außen angebrachte elektrische Reizung zu beeinflussen. Mit Hilfe der GVS konnte gezeigt werden, dass sich die Wahrnehmungschwelle für vestibuläre Bewegungsreize künstlich herabsetzen lässt (Keywan, Wuehr et al. 2018). Unter einer vergleichbaren Reizung zeigte sich zudem eine Verbesserung der vestibulospinalen (Wuehr, Boerner et al. 2018) und vestibulookulären Reflexfunktionen (Serrador, Deegan et al. 2018). Die vestibuläre stochastische Resonanz wurde in einer vorangegangenen Studie bereits therapeutisch

genutzt, um das statische Haltungsgleichgewicht von Patienten mit BVP zu verbessern. Dabei zeigte sich unter Behandlung mit einer rauschhaften GVS eine deutlich subjektive sowie objektiv messbare Stabilisierung der Haltungskontrolle bei Patienten (Iwasaki, Yamamoto et al. 2014).

5. Kumulative Dissertation

Aufbauend auf den ersten vielversprechenden Studienergebnissen zur therapeutischen Wirkung einer vestibulären Rauschstimulation wurde in den Studien dieses Promotionsvorhabens der therapeutische Einfluss der Stimulation auf die Gangstabilität bei gesunden Probanden und bei Patienten mit BVP untersucht.

Folgende Forschungsfragen standen dabei im Fokus:

(1) Treten grundsätzlich während des Gehens vestibuläre Eingangssignale auf, die unterhalb der vestibulären Verarbeitungsschwelle liegen und somit durch die zusätzliche Rauschreizung verstärkt werden können?

(2) Kommt es durch die rauschbedingte Verstärkung vestibulärer Eingangssignale zu einer subjektiven und objektiv messbaren Stabilisierung der Gangkontrolle bei gesunden Personen und Patienten mit bilateraler Vestibulopathie?

Zunächst wurde der Einfluss der vestibulären Rauschreizung auf das Gangverhalten von gesunden Probanden in der unter dem Titel „Noise-enhanced vestibular input improves dynamic walking stability in healthy subjects“ veröffentlichten Studie untersucht. Hierfür wurde das spatiotemporale Gangbild sowie das subjektive Balanceempfinden von 17 gesunden Probanden auf einem Laufband während einer schwachen, nicht wahrnehmbaren vestibulären Rauschstimulation (GVS) im Vergleich zu einer Scheinstimulation (Placebokontrolle) gemessen. Um die Stabilitätskontrolle künstlich zu erschweren, erfolgte die Gangtestung mit geschlossenen Augen bei langsamer, mittlerer und schneller

Geschwindigkeit. Zugleich wurden die während des Gehens auftretenden vestibulären Eingangssignale mit Hilfe eines am Kopf befestigten Beschleunigungssensors gemessen.

In einer Folgestudie, die unter dem Titel „Noisy galvanic vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy“ veröffentlicht wurde, wurde die Wirkung der vestibulären Rauschstimulation auf die subjektive und objektiv messbare Stabilitätsregulation während des Gehens bei 13 Patienten mit BVP untersucht. Die Untersuchungsbedingungen entsprachen im Wesentlichen der initialen Studie mit gesunden Probanden. Die Gangtestung der Patienten erfolgte jedoch auf Grund des erhöhten Sturzrisikos während des Gehens mit offenen Augen.

6. **Noise-Enhanced Vestibular Input Improves DynamicWalking Stability in Healthy Subjects**
   M.Wuehr, E. Nusser, S. Krafczyk, A. Straube, T. Brandt, K. Jahn, R. Schniepp

Brain Stimulation 9 (2016) 109–116

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Noise-Enhanced Vestibular Input Improves Dynamic Walking Stability in Healthy Subjects

M. Wuehr [a,*,1], E. Nusser [b,1], S. Krafczyk [a,b], A. Straube [a,b], T. Brandt [a,c], K. Jahn [a,d], R. Schniepp [a,b]

[a] German Center for Vertigo and Balance Disorders, University of Munich, Germany
[b] Department of Neurology, University of Munich, Germany
[c] Institute for Clinical Neuroscience, University of Munich, Germany
[d] Schoen Klinik Bad Aibling, Germany

ARTICLE INFO

Article history:
Received 31 May 2015
Received in revised form 28 August 2015
Accepted 31 August 2015
Available online

Keywords:
Galvanic vestibular stimulation
Stochastic resonance
Vestibular feedback
Gait stability
Gait variability

ABSTRACT

Background: White noise galvanic vestibular stimulation (GVS) is thought to enhance the sensitivity of vestibular organs.
Objective: To examine the effects of noise-enhanced vestibular input on the walking performance in healthy subjects walking with eyes closed.
Methods: Walking performance of 17 healthy subjects (mean age 28.8 ± 1.7 years) at slow, preferred, and fast speeds was examined during three different conditions: (1) walking with eyes open (EO) as baseline condition, (2) walking with eyes closed and sham noisy GVS (EC), and (3) walking with eyes closed and non-zero amplitude noisy GVS set to 80% of the individual sensory threshold for GVS (EC-GVS). Ten gait parameters were examined: stride time, stride length, base of support, swing time percentage, double support time percentage as well as gait asymmetry, bilateral phase coordination and the coefficient of variation (CV) of stride time, stride length and base of support.
Results: Noisy GVS improved stride time CV by 36% ($p < 0.034$), stride length CV by 31% ($p < 0.037$), base of support CV by 14% ($p < 0.009$), and bilateral phase coordination by 23% ($p < 0.034$). The ameliorating effects of noisy GVS on locomotion function were primarily observable during slow walking speeds.
Conclusion: Noise-enhanced vestibular input is effective in improving locomotion function and is accompanied by a subjectively felt improvement of walking balance. It predominantly targets the variability and bilateral coordination characteristics of the walking pattern, which are critically linked to dynamic walking stability. Noisy GVS might present an effective treatment option to improve walking performance in patients with bilateral vestibular dysfunction.

Introduction

Maintaining dynamic stability during walking relies on accurate sensory feedback from the visual, vestibular and somatosensory systems. Sensory feedback control during walking is thought to be important for adjusting stride-to-stride trajectories to maintain balance and for smoothing unintended irregularities during motor execution [1,2]. Consequently, an impairment or loss in either of the sensory feedback modalities results in a decreased walking stability accompanied by an increased risk to fall [3–5]. The ability to restore sensory function required for a stable walking performance is therefore a desirable treatment option for patients with sensory deficits.

Previous research has demonstrated that information processing in a variety of sensory systems can be enhanced by adding an imperceptible amount of noise to the sensory system [6]. The rationale behind this phenomenon is a mechanism known as stochastic resonance wherein the response of a nonlinear system to input signals can be optimized by the presence of a particular non-zero level of noise [7]. By means of this mechanism, especially weak subthreshold sensory signals have been shown to be boosted above the detection threshold by resonating with added white noise [6]. Stochastic resonance has further been used to improve sensory feedback involved in postural control. Accordingly, it was shown that a subthreshold noise input to the somatosensory as well as the vestibular system is able to improve static postural equilibrium in healthy subjects standing with eyes closed as well as in patients with sensory deficits [8–10].

* Corresponding author. Tel.: +49 89 7095 3671; fax: +49 89 7095 6671.
E-mail address: Max.Wuehr@med.uni-muenchen.de (M. Wuehr).
[1] Authors contributed equally.

1935-861X/
http://dx.doi.org/10.1016/j.brs.2015.08.017

The purpose of the present study was to evaluate whether noise-enhanced input from the vestibular system is able to improve walking stability in healthy subjects walking with eyes closed. A positive evaluation of this approach would offer a future treatment option for restoring gait stability in patients with a bilateral vestibular dysfunction. To test this option, we used galvanic vestibular stimulation (GVS), which is a known procedure to electrically stimulate vestibular afferents [11]. GVS was applied as imperceptible amounts of white noise into the vestibular system of healthy subjects when walking with eyes closed. Head kinematics while walking were measured in order to estimate the magnitude of vestibular inputs during the stimulation trials. The effects of noisy GVS on the walking performance were tested at different walking speeds (i.e., slow, preferred and fast) and it was hypothesized that noisy GVS would predominantly affect slow locomotion modes that are thought to critically rely on sensory feedback control [3,5,12,13]. We further hypothesized that noisy GVS would primarily influence the stride-to-stride fluctuation and bilateral coordination characteristics of the walking pattern, which have been shown to be most sensitive to alterations in sensory feedback control [3–5] and which are closely linked to dynamic gait stability [14,15].

Materials and methods

Subjects

Seventeen healthy subjects (seven females/ten males; mean age 28.8 ± 1.7 years) participated in the study (Table 1). None of the participants reported any auditory, vestibular, neurologic, cardio-vascular or orthopedic disorders. All subjects had normal or corrected-to-normal vision.

Galvanic vestibular stimulation

GVS was delivered by a battery-driven constant current stimulator (neuroConn®, Ilmenau, Germany) through conductive-rubber electrodes, placed in two saline-soaked sponges placed over left and right mastoid process behind the ears. The electrical signal consisted of zero-mean Gaussian white noise within a frequency range of 0–30 Hz [9,16]. The GVS intensity (i.e., peak amplitude) was set to 80% of cutaneous threshold, which has been previously shown to be the optimal amplitude of noisy GVS in healthy subjects [9]. The sensory threshold was determined using stepwise method [17,18]: Accordingly, starting from a current level of 20 μA, noisy test stimuli were delivered for 10 s periods with stepwise increases (20 μA) until participants perceived a mild tingling sensation at the electrode sites. This procedure was then repeated to confirm the sensory threshold. For the GVS sham condition the signal intensity was set to 0 μA.

Table 1
Characteristics, stimulation amplitudes, and walking velocities of the study collective (mean ± SEM).

Gender	7 females/10 males
Age	28.8 ± 1.7
Height (cm)	175.8 ± 2.3
Weight (kg)	71.8 ± 3.7
Leg length (cm)	91.8 ± 1.1
Threshold of sensation (μA)	405.3 ± 35.6
GVS amplitude (μA)	324.2 ± 28.5
Slow walking speed (m/s)	0.3 ± 0.1
Preferred walking speed (m/s)	1.4 ± 0.1
Fast walking speed (m/s)	1.7 ± 0.1

GVS – galvanic vestibular stimulation.

Procedures

Initially, the preferred walking speed of each subject was determined during normal over-ground locomotion on a 6.7 m long, pressure-sensitive carpet system (GAITRite®, CIR System, Havertown, USA) with a sampling rate of 120 Hz. Subsequently, steady-state locomotion was measured on a 1.6 m long, pressure-sensitive treadmill system (Zebris®, Isny, Germany; h/p/cosmos®, Nussdorf-Traunstein, Germany) with a sampling rate of 100 Hz. To derive an estimate of vestibular inputs during locomotion, head kinematics were measured via a three-dimensional inertial sensor (APDM, Inc., Portland, OR) with a sampling rate of 128 Hz, strapped to the head in orientation parallel to Reid's base line.

Three different conditions were examined on the treadmill system. First one baseline condition: (1) walking with eyes open (EO), subsequently two stimulation conditions: (2) walking with eyes closed and zero-amplitude sham GVS (EC) and (3) walking with eyes closed and non-zero-amplitude GVS (EC-GVS). The stimulation conditions were tested in a randomized order and subjects were blinded to the stimulation protocol. After completion of the three test conditions, subjects were asked whether they felt any change in walking balance (no change, improvement or deterioration) between the two stimulation conditions. This procedure was repeated for three different walking speeds in a randomized order: preferred walking speed (PWS), slow walking speed (25% of PWS), and fast walking speed (125% of PWS) – resulting in a total of nine trials. The recording duration of each of the nine trials was 2 minutes. Before each recording, participants were given 1 minute to adapt to the preset treadmill speed. Between trials, participants were given at least 2 minutes to recover (Fig. 1).

Data analysis

Two different groups of gait parameters were analyzed. First, five parameters characterizing the mean spatiotemporal gait pattern: stride time, stride length, base of support, swing time percentage, double support time percentage. Second, five parameters quantifying the bilateral walking coordination and the gait variability: gait asymmetry (GA)[1] [19] and bilateral phase synchronization by using the phase coordination index (PCI)[2] [20] as well as the coefficient of variation (CV) of stride time, stride length and base of support. Head kinematics were analyzed by calculating the root mean square (RMS) of head angular velocity in roll, yaw, and pitch plane.

Statistical analysis

Data are reported as mean ± SEM. The effects of each dependent variable were analyzed using a two-way repeated measurement analysis of variance (rmANOVA) and a Bonferroni post hoc analysis with walking speed (slow, preferred, fast) and sensory condition (EO, EC, EC-GVS) as factors. Significant interaction effects were further decomposed into simple main effects. Results were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS (Version 20.0; IBM Corp., Armonk, NY).

[1] Gait asymmetry (GA) was quantified by the following formula: $GA = 100 \times \left| ln \frac{SSWT}{LSWT} \right|$, where SSWT and LSWT denote the mean swing times for the leg with the short and with the long mean swing time, respectively.

[2] The phase coordination index (PCI) was quantified by first calculating the phase φ_i of the ith heel strike defined as: $\varphi_i = 360° \times \frac{t_{Si} - t_{Li}}{t_{L(i+1)} - t_{Li}}$, where t_{Si} and t_{Li} stand for the times of the ith heel strike of the leg with the short and long mean swing times, respectively and $t_{L(i+1)} > t_{Si} > t_{Li}$. The PCI is then calculated by: $PCI = 100 \times \frac{\varphi_{ABS}}{180°} + \varphi_{CV}$, where φ_{ABS} is given by: $\varphi_{ABS} = \overline{|\varphi_i - 180°|}$ and φ_{CV} is the coefficient of variation of the time series φ_i.

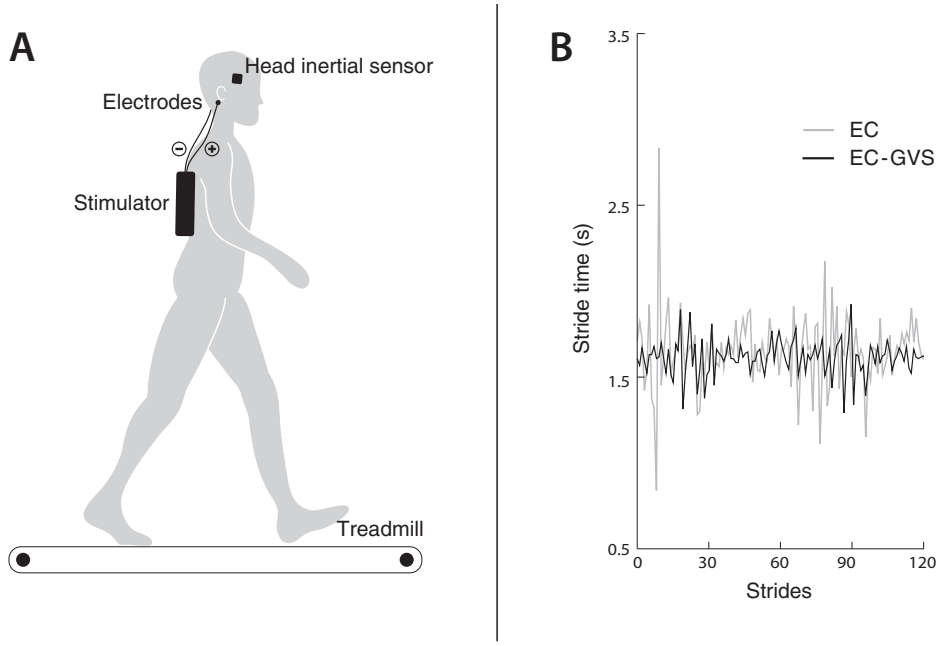


Figure 1. (**A**) Experimental setup. Noisy galvanic vestibular stimulation was applied with electrodes on the left and right mastoid process behind the ears by a portable stimulator. Subjects walked at three speeds (slow, preferred and fast) on a pressure-sensitive treadmill. Head motion was measured via a three-dimensional inertial sensor strapped to the head in orientation parallel to Reid's base line. (**B**) Stride time series of a representative individual while walking slowly with eyes closed and zero-amplitude noisy GVS (EC; gray line) and while walking slowly with eyes closed and noisy GVS at an intensity of 300 μA (EC-GVS; black line).

Results

The rmANOVA results are presented in Table 2. The mean threshold of sensation for GVS was 405.3 ± 35.6 μA. Accordingly the mean applied simulation amplitude of noisy GVS was 324.2 ± 28.5 μA (corresponding to 80% of the threshold). The mean walking speeds examined were 0.3 ± 0.1 m/s for slow walking, 1.4 ± 0.1 m/s for preferred walking, and 1.7 ± 0.1 m/s for fast walking (Table 1).

Stimulation effects on mean spatiotemporal parameters

Compared to baseline condition (i.e., EO), walking with eyes closed and zero-amplitude GVS (i.e., EC) resulted in significantly shorter stride times for slow and preferred walking and in significantly smaller stride lengths during all walking speeds (Fig. 2A,B). All other mean spatiotemporal gait parameters did not show any significant alterations for walking with EC compared to EO. None of the mean spatiotemporal gait parameters did show any significant response to noisy GVS (i.e., EC-GVS).

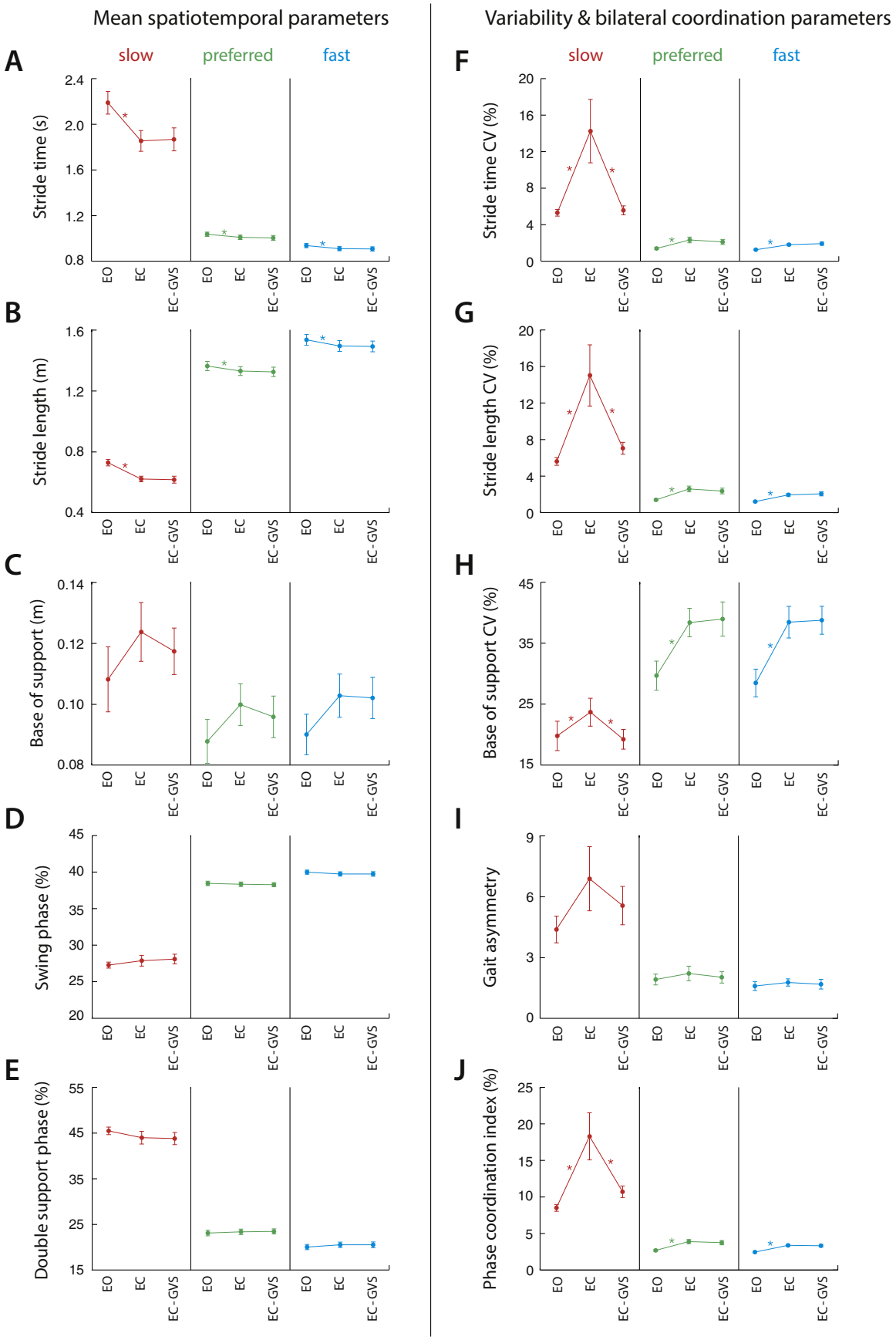
Stimulation effects on variability and bilateral coordination parameters

Compared to baseline condition (i.e., EO), walking with eyes closed and zero-amplitude GVS (i.e., EC) resulted in a significant increase of stride time CV, stride length CV, and base of support CV at all walking speeds and additionally a decrease in bilateral phase coordination during slow walking (Fig. 2F–J). Turning on noisy GVS

Table 2
Repeated measurement ANOVA results.

	Speed (SWS | PWS | FWS)	Condition (EO | EC | EC-GVS)	Speed × condition
Mean spatiotemporal gait parameters			
Stride time	**$F_{2,32}$ = 147.0, p < 0.001**	**$F_{2,32}$ = 45.8, p < 0.001**	**$F_{4,64}$ = 28.6, p < 0.001**
Stride length	**$F_{2,32}$ = 652.2, p < 0.001**	**$F_{2,32}$ = 60.7, p < 0.001**	**$F_{4,64}$ = 9.7, p = 0.045**
Base of support	**$F_{2,32}$ = 11.1, p = 0.003**	**$F_{2,32}$ = 10.0, p = 0.003**	$F_{4,64}$ = 0.4, p = 0.735
Swing phase	**$F_{2,32}$ = 680.4, p < 0.001**	$F_{2,32}$ = 0.3, p = 0.758	$F_{4,64}$ = 0.2, p = 0.149
Double support phase	**$F_{2,32}$ = 725.0, p < 0.001**	$F_{2,32}$ = 0.4, p = 0.668	$F_{4,64}$ = 2.7, p = 0.081
Variability and bilateral coordination gait parameters			
Stride time CV	**$F_{2,32}$ = 32.5, p < 0.001**	**$F_{2,32}$ = 6.7, p = 0.018**	**$F_{4,64}$ = 5.1, p = 0.037**
Stride length CV	**$F_{2,32}$ = 38.3, p < 0.001**	**$F_{2,32}$ = 8.2, p = 0.009**	**$F_{4,64}$ = 5.3, p = 0.032**
Base of support CV	**$F_{2,32}$ = 37.0, p < 0.001**	**$F_{2,32}$ = 15.3, p < 0.001**	**$F_{4,64}$ = 5.8, p = 0.001**
Gait asymmetry	**$F_{2,32}$ = 33.1, p < 0.001**	$F_{2,32}$ = 1.5, p = 0.238	$F_{4,64}$ = 0.9, p = 0.416
Phase coordination index	**$F_{2,32}$ = 62.0, p < 0.001**	**$F_{2,32}$ = 8.9, p = 0.007**	**$F_{4,64}$ = 5.6, p = 0.025**
Head kinematics			
Roll angular velocity RMS	**$F_{2,32}$ = 15.9, p < 0.001**	**$F_{2,32}$ = 14.3, p = 0.001**	$F_{4,64}$ = 0.6, p = 0.595
Yaw angular velocity RMS	**$F_{2,32}$ = 12.5, p < 0.001**	$F_{2,32}$ = 2.5, p = 0.119	$F_{4,64}$ = 0.4, p = 0.747
Pitch angular velocity RMS	**$F_{2,32}$ = 67.1, p < 0.001**	**$F_{2,32}$ = 9.3, p = 0.002**	$F_{4,64}$ = 2.1, p = 0.115

Significant effects are marked in bold.
SWS – slow walking speed, PWS – preferred walking speed, FWS – fast walking speed, EO – walking with eyes open, EC – walking with eyes closed, EC-GVS – walking with eyes closed and noisy galvanic stimulation.


Mean spatiotemporal parameters
Variability & bilateral coordination parameters
slow
preferred
fast
A
Stride time (s)
B
Stride length (m)
C
Base of support (m)
D
Swing phase (%)
E
Double support phase (%)
F
Stride time CV (%)
G
Stride length CV (%)
H
Base of support CV (%)
I
Gait asymmetry
J
Phase coordination index (%)
EO
EC
EC-GVS

during walking with eyes closed (i.e., EC-GVS) caused significant improvements of all examined variability and bilateral coordination parameters. This effect was only observable during walking with slow speed. Stride time CV decreased by 35.6 ± 7.6% ($p < 0.034$), stride length CV by 30.7 ± 8.1% ($p < 0.037$), base of support CV by 13.7 ± 7.1% ($p < 0.009$), and PCI by 23.2 ± 8.9% ($p < 0.034$) (Fig. 2F–J). The fact that the ameliorating effect of noisy GVS on walking balance was primarily observable during slow walking was also reflected in the participants' reports on subjective improvement during noisy GVS. For slow walking, 65% of the participants reported a subjective improvement in walking balance due to noisy GVS compared to only 35% during preferred walking and 18% during fast walking.

Stimulation effects on head kinematics

Compared to baseline condition (i.e., EO), walking with eyes closed and zero-amplitude GVS (i.e., EC) resulted in significantly decreased RMS for head roll and pitch angular velocity during all walking velocities. RMS of head angular velocity in all axes of rotation did not show any significant response to GVS (i.e., EC-GVS) (Fig. 3A–C).

Discussion

The present study examined the effects of noise-enhanced vestibular input on the walking performance of healthy subjects walking with eyes closed. We observed that decreased dynamic stability during walking with eyes closed could be significantly improved by applying imperceptible levels of white noise GVS. This ameliorating effect of noise-enhanced vestibular input depended on the walking speed and predominantly improved the stride-to-stride fluctuation and bilateral coordination characteristics of the walking pattern, which are closely linked to dynamic gait stability. The relevance of these findings will be discussed in two parts: (1) Influence of noise-enhanced vestibular input on dynamic walking stability and (2) putative mechanism and clinical application of noise-enhanced vestibular input.

Influence of noise-enhanced vestibular input on dynamic gait stability

In conformance with previous studies, we observed that deprivation of visual feedback resulted in a decrease of dynamic walking stability during slow walking indicated by increased fore-aft (i.e., stride time and stride length) and medio-lateral (i.e., base of support) stride-to-stride fluctuations, a more variable bilateral phase coordination and a less symmetric gait pattern [3]. It is commonly believed that alterations in walking performance due to a loss of vision cannot be fully compensated by somatosensory and vestibular information [21]. However, the present results demonstrate that noise-enhanced input from the vestibular system is able to compensate for visual deprivation caused gait alterations by up to ~35%. Vestibular feedback in gait control is thought to be primarily required for stabilizing the head to ensure stable gaze control during locomotion and for spatial orientation in navigational tasks [22–24]. More recently, vestibular information was also suggested to play a critical role in maintaining dynamic walking stability by fine-tuning the timing and magnitude of foot displacement in a phase-dependent manner [25–27]. Correspondingly disturbed vestibular feedback typically results in increased stride-to-stride variability, i.e., an impaired walking stability [4,28]. The observed effects of noisy GVS on the walking performance support the latter aspect of vestibular locomotion function, i.e., its contributions to stabilize the walking pattern. Noise-enhanced vestibular input significantly decreased the fore-aft and medio-lateral stride-to-stride fluctuations and improved the bilateral phase coordination and left–right symmetry of the walking pattern. Decreased gait fluctuations in the fore-aft and medio-lateral walking plane, as well as enhanced bilateral walking coordination, have been linked to an increased dynamic walking stability and a lower risk to fall [14,15,29,30]. Noisy GVS induced changes in walking performance were further associated to a subjectively felt improvement of walking balance in participants. In contrast, noisy GVS had little to no effect on the mean spatiotemporal walking pattern, supporting the view that it is the stride-to-stride dynamics of walking that are primarily sensitive to alterations in sensory feedback [5,31].

Moreover, we observed that noise-enhanced vestibular input influenced the walking performance in a speed-dependent manner. Noisy GVS led to enhanced dynamic walking stability predominantly during slow walking but had hardly any effect on preferred and fast walking modes. This observation corresponds to the growing evidence of a speed-dependent role of sensory feedback in locomotion control. Accordingly, the impact of a vestibular, visual or somatosensory loss or perturbation decreases with increasing walking speed [3–5,12,24]. Functional imaging studies could further confirm that sensory cortex activity is decreased at faster walking modes [13,32]. Active sensory feedback control is therefore thought to be primarily necessary for balance control during slow locomotion, whereas internal feedforward commands from spinal central pattern generators are likely to dominate balance control at fast locomotion modes [33].

Putative mechanism and clinical application of noise-enhanced vestibular input

The putative mechanism underlying noise-enhanced vestibular input is thought to be stochastic resonance, according to which a system's ability to detect weak signals can be enhanced by addition of a random interference, i.e., white noise [6,7]. Accordingly an appropriate level of noise, delivered via a white noise GVS, might facilitate weak signal detection in the vestibular system via small changes in receptor potentials that lower the detection threshold of vestibular neurons [9,10]. Since the phenomenon of stochastic resonance does only occur in nonlinear systems, it is important to note that vestibular signal processing has been shown to be essentially nonlinear [34,35].

Vestibular afferents exhibit detection thresholds for angular velocities ranging from 4 deg/s for regular afferents to 8 deg/s for irregular afferents [34]. GVS has been shown to predominantly activate the irregular primary afferents of the vestibular system [11]. Previous studies examining the effect stochastic resonance for the vestibular system have considered behavioral tasks, i.e. quiet standing, in which the baseline vestibular inputs were below vestibular detection thresholds [9,10,16]. To test whether subthreshold vestibular input is also present during locomotion at different velocities, we measured and analyzed head kinematics for each walking trial. Our results show that RMS of head angular velocity in all axes of rotation is below or in the range of established vestibular detection

Figure 2. Gait changes in response to noisy GVS. Mean ± SEM of the 10 examined gait parameters (**A–E**: mean spatiotemporal parameters; **F–J**: variability and bilateral coordination parameters) during baseline condition, i.e., walking with eyes open (EO) and the two simulation conditions, i.e., walking with eyes closed with sham GVS (EC) and walking with eyes closed with non-zero amplitude noisy GVS (EC-GVS). Noisy GVS particularly improves the variability and bilateral coordination characteristics of the walking pattern and is predominantly effective during slow walking. *Significant change in gait parameter between conditions.

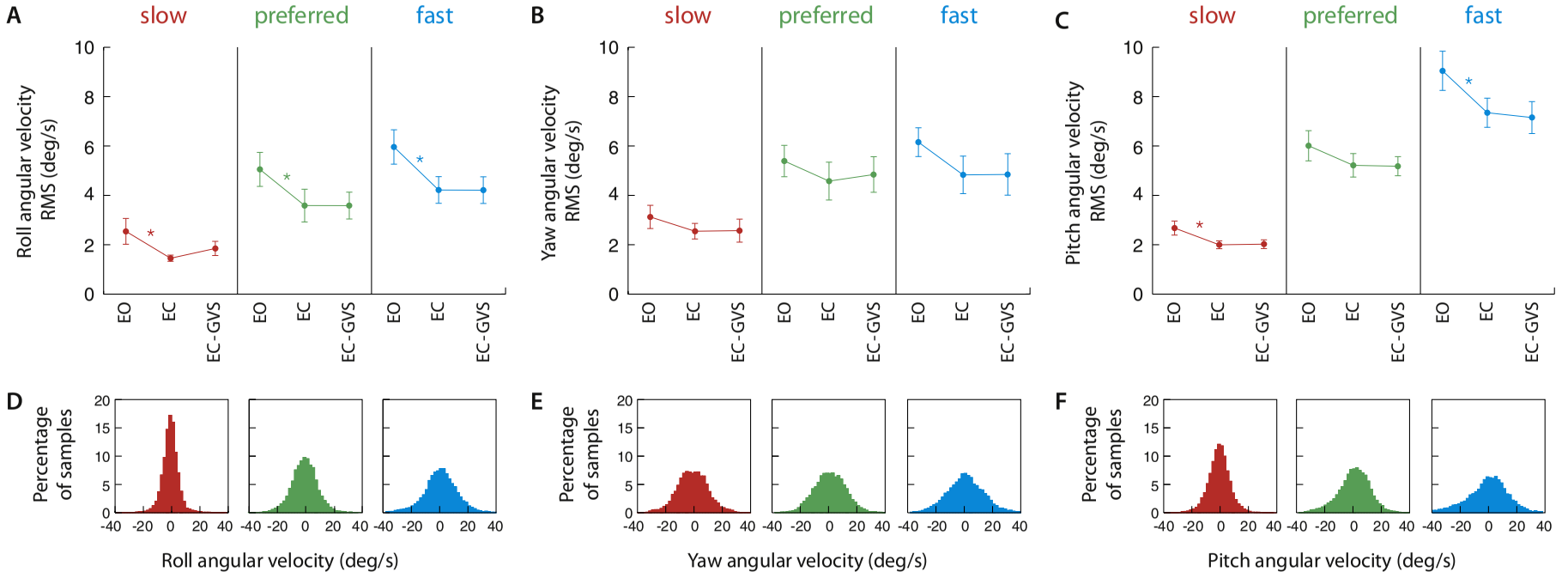


Figure 3. Head kinematics in response to noisy GVS. Mean ± SEM of the root mean square (RMS) of head angular velocity in roll plane (**A**), yaw plane (**B**), and pitch plane (**C**) during baseline condition, i.e., walking with eyes open (EO) and the two simulation conditions, i.e., walking with eyes closed with sham GVS (EC) and walking with eyes closed with non-zero amplitude noisy GVS (EC-GVS). Corresponding distribution of head angular velocity for the condition EC-GVS in roll plane (**D**), yaw plane (**E**), and pitch plane (**E**). Each histogram is based 17,000 data points averaged over 17 subjects. Bin width: 2 deg/s. *Significant change head angular velocity RMS between conditions.

thresholds for all examined walking speeds (Fig. 3A–C). Average distributions of head angular velocities recorded during the stimulation trials further demonstrate that a considerable amount of vestibular inputs were subthreshold especially for slow velocities, where in average 72% of head angular velocities were below 8 deg/s. However, this amount decreases for faster walking modes to in average 59% for preferred and 49% for fast walking speeds (Fig. 3D–F). This might also provide an explanation for the primary effect of noisy GVS during slow walking speeds. During walking with eyes closed we found reduced head kinematics in conformance with previous studies that observed decreased head peak angular velocities due to deprivation of visual feedback [22,36]. Reduced head kinematics during walking with eyes closed have been interpreted to reflect either a tighter vestibular and proprioceptive control of head motion [22,36] or an enhanced locking of the head on the trunk, which would reduce the degrees of freedom of the head–neck system [22]. In favor of the second hypothesis, we did not find any beneficial effect on head stabilization in response to noise-enhanced vestibular input when walking with eyes closed.

In the past, noise-enhanced vestibular input has been demonstrated to improve static postural equilibrium in healthy subjects as well as in patients with bilateral vestibular dysfunction possibly via a facilitation of vestibulospinal reflexes [9,10]. There is also first evidence for a positive impact of noisy GVS on ocular–motor function, in particular improved ocular counter-roll reflexes in response to whole-body tilt [37]. However, further studies are required to test whether noisy GVS can also improve gaze stabilization during locomotion. The results presented here complement these findings by demonstrating that noise-enhanced input from the vestibular system is capable of improving postural stability during dynamic walking tasks. These beneficial effects of noise-enhanced vestibular input might also entail important clinical relevance. Decrements in vestibular function due to aging or disease are accompanied by postural disequilibrium during standing and walking and typically result in a higher risk to fall [38,39]. Currently, there is no effective treatment option available for subjects with bilateral vestibular dysfunction except rehabilitation [40]. In this context, noisy GVS might act as a sensory prosthesis, which increases the sensitivity of residual vestibular afferents in patients with an intact vestibular nerve to improve their walking performance and reduce their risk to fall [8,41]. Further studies are however required to examine the here observed effects in patients with bilateral vestibular dysfunction. Finally, there is also first evidence that noise-enhanced vestibular input can improve motor function in patients with Parkinson's disease and other neurodegenerative diseases [16,42].

Ethical standard

This study has been approved by the appropriate Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Acknowledgements

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG (JA1087/1-1), the German Hertie Foundation, and the German Federal Ministry of Education and Research (01EO1401).

References

[1] Gandevia S, Burke D. Does the nervous system depend on kinesthetic information to control natural limb movements? Behav Brain Sci 1992;15:614.
[2] Nashner LM. Balance adjustments of humans perturbed while walking. J Neurophysiol 1980;44:650–64.
[3] Wuehr M, Schniepp R, Pradhan C, Ilmberger J, Strupp M, Brandt T, et al. Differential effects of absent visual feedback control on gait variability during different locomotion speeds. Exp Brain Res 2013;224:287–94.
[4] Schniepp R, Wuehr M, Neuhaeusser M, Kamenova M, Dimitriadis K, Klopstock T, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. Mov Disord 2012;27:125–31.
[5] Wuehr M, Schniepp R, Schlick C, Huth S, Pradhan C, Dieterich M, et al. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. Gait Posture 2014;39:852–8.
[6] Moss F, Ward LM, Sannita WG. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol 2004;115:267–81.
[7] Collins J, Chow CC, Imhoff TT. Stochastic resonance without tuning. Nature 1995;376:236–8.
[8] Priplata AA, Niemi JB, Harry JD, Lipsitz LA, Collins JJ. Vibrating insoles and balance control in elderly people. Lancet 2003;362:1123–4.
[9] Iwasaki S, Yamamoto Y, Togo F, Kinoshita M, Yoshifuji Y, Fujimoto C, et al. Noisy vestibular stimulation improves body balance in bilateral vestibulopathy. Neurology 2014;82:969–75.
[10] Mulavara AP, Fiedler MJ, Kofman IS, Wood SJ, Serrador JM, Peters B, et al. Improving balance function using vestibular stochastic resonance: optimizing stimulus characteristics. Exp Brain Res 2011;210:303–12.
[11] Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. J Appl Physiol 2004;96:2301–16.
[12] Brandt T, Strupp M, Benson J. You are better off running than walking with acute vestibulopathy. Lancet 1999;354:746.
[13] Jahn K, Deutschländer A, Stephan T, Strupp M, Wiesmann M, Brandt T. Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging. Neuroimage 2004;22:1722–31.
[14] Hausdorff JM. Gait variability: methods, modeling and meaning. J Neuroeng Rehabil 2005;2:19.
[15] Krasovsky T, Banina MC, Hacmon R, Feldman AG, Lamontagne A, Levin MF. Stability of gait and interlimb coordination in older adults. J Neurophysiol 2012;107:2560–9.
[16] Samoudi G, Jivegard M, Mulavara AP, Bergquist F. Effects of stochastic vestibular galvanic stimulation and LDOPA on balance and motor symptoms in patients with Parkinson's disease. Brain Stimul 2014;8(3):474–80.
[17] Wilkinson D, Nicholls S, Pattenden C, Kilduff P, Milberg W. Galvanic vestibular stimulation speeds visual memory recall. Exp Brain Res 2008;189:243–8.
[18] Wilkinson D, Ko P, Kilduff P, McGlinchey R, Milberg W. Improvement of a face perception deficit via subsensory galvanic vestibular stimulation. J Int Neuropsychol Soc 2005;11:925–9.
[19] Plotnik M, Bartsch RP, Zeev A, Giladi N, Hausdorff JM. Effects of walking speed on asymmetry and bilateral coordination of gait. Gait Posture 2013;38(4):864–9.
[20] Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. Exp Brain Res 2007;181:561–70.
[21] Hallemans A, Beccu S, Van Loock K, Ortibus E, Truijen S, Aerts P. Visual deprivation leads to gait adaptations that are age- and context-specific: I. Step-time parameters. Gait Posture 2009;30:55–9.
[22] Pozzo T, Berthoz A, Lefort L. Head stabilization during various locomotor tasks in humans. Exp Brain Res 1990;82:97–106.
[23] Fitzpatrick RC, Wardman DL, Taylor JL. Effects of galvanic vestibular stimulation during human walking. J Physiol 1999;517:931–9.
[24] Jahn K, Strupp M, Schneider E, Dieterich M, Brandt T. Differential effects of vestibular stimulation on walking and running. Neuroreport 2000;11:1745–8.
[25] Bent LR, Inglis JT, McFadyen BJ. When is vestibular information important during walking? J Neurophysiol 2004;92:1269–75.
[26] Dakin CJ, Inglis JT, Chua R, Blouin JS. Muscle-specific modulation of vestibular reflexes with increased locomotor velocity and cadence. J Neurophysiol 2013;110:86–94.
[27] Blouin JS, Dakin CJ, van den Doel K, Chua R, McFadyen BJ, Inglis JT. Extracting phase-dependent human vestibular reflexes during locomotion using both time and frequency correlation approaches. J Appl Physiol 2011;111:1484–90.
[28] van Schooten KS, Sloot LH, Bruijn SM, Kingma H, Meijer OG, Pijnappels M, et al. Sensitivity of trunk variability and stability measures to balance impairments induced by galvanic vestibular stimulation during gait. Gait Posture 2011;33:656–60.
[29] Brach JS, Berlin JE, Vanswearingen JM, Newman AB, Studenski SA. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. J Neuroeng Rehabil 2005;2:2–21.
[30] Wuehr M, Pradhan C, Brandt T, Jahn K, Schniepp R. Patterns of optimization in single- and inter-leg gait dynamics. Gait Posture 2014;39:733–8.
[31] Dingwell JB, Cusumano JP, Sternad D, Cavanagh PR. Slower speeds in patients with diabetic neuropathy lead to improved local dynamic stability of continuous overground walking. J Biomech 2000;33:1269–77.
[32] Jahn K, Deutschländer A, Stephan T, Kalla R, Hüfner K, Wagner J, et al. Supraspinal locomotor control in quadrupeds and humans. Prog Brain Res 2008;171:353–62.
[33] Lambert FM, Combes D, Simmers J, Straka H. Gaze stabilization by efference copy signaling without sensory feedback during vertebrate locomotion. Curr Biol 2012;22:1649–58.
[34] Sadeghi SG, Chacron MJ, Taylor MC, Cullen KE. Neural variability, detection thresholds, and information transmission in the vestibular system. J Neurosci 2007;27:771–81.

[35] Massot C, Schneider AD, Chacron MJ, Cullen KE. The vestibular system implements a linear-nonlinear transformation in order to encode self-motion. PLoS Biol 2012;10:e1001365.
[36] Cromwell RL, Newton RA, Forrest G. Influence of vision on head stabilization strategies in older adults during walking. J Gerontol A Biol Sci Med Sci 2002;57:M442–8.
[37] Serrador JM, Geraghty MC, Deegan BM, Wood SJ. Enhancing vestibular function by imperceptible electrical stimulation. J Vestib Res 2011;21:101–3.
[38] Herdman SJ, Blatt P, Schubert MC, Tusa RJ. Falls in patients with vestibular deficits. Am J Otol 2000;21:847–51.
[39] Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. Neurosci Lett 2009;465:10–15.
[40] Guinand N, Boselie F, Guyot JP, Kingma H. Quality of life of patients with bilateral vestibulopathy. Ann Otol Rhinol Laryngol 2012;121:471–7.
[41] Chatterjee M, Robert ME. Noise enhances modulation sensitivity in cochlear implant listeners: stochastic resonance in a prosthetic sensory system? J Assoc Res Otolaryngol 2001;2:159–71.
[42] Pan W, Soma R, Kwak S, Yamamoto Y. Improvement of motor functions by noisy vestibular stimulation in central neurodegenerative disorders. J Neurol 2008;255:1657–61.

7. Noisy vestibular stimulation improves dynamic walking stability in bilateralvestibulopathy

M. Wuehr, E. Nusser, J. Decker, S. Krafczyk, A. Straube, T. Brandt, K. Jahn, R. Schniepp,

Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy

Max Wuehr, PhD
Eva Nusser
Julian Decker
Siegbert Krafczyk, PhD
Andreas Straube, MD
Thomas Brandt, MD
Klaus Jahn, MD
Roman Schniepp, MD

Correspondence to
Dr. Wuehr:
Max.Wuehr@med.uni-muenchen.de

ABSTRACT

Objective: To examine the effects of imperceptible levels of white noise galvanic vestibular stimulation (nGVS) on dynamic walking stability in patients with bilateral vestibulopathy (BVP).

Methods: Walking performance of 13 patients with confirmed BVP (mean age 50.1 ± 5.5 years) at slow, preferred, and fast speeds was examined during walking with zero-amplitude nGVS (sham trial) and nonzero-amplitude nGVS set to 80% of the individual cutaneous threshold for GVS (nGVS trial). Eight standard gait measures were analyzed: stride time, stride length, base of support, double support time percentage as well as the bilateral phase coordination index, and the coefficient of variation (CV) of stride time, stride length, and base of support.

Results: Compared to the sham trial, nGVS improved stride time CV by 26.0% ± 8.4% ($p < 0.041$), stride length CV by 26.0% ± 7.7% ($p < 0.029$), base of support CV by 27.8% ± 2.9% ($p < 0.037$), and phase coordination index by 8.4% ± 8.8% ($p < 0.013$). The nGVS effects on walking performance were correlated with subjective ratings of walking balance ($\rho = 0.79$, $p < 0.001$). Effect of nGVS on walking stability was most pronounced during slow walking.

Conclusions: In patients with BVP, nGVS is effective in improving impaired gait performance, predominantly during slower walking speeds. It primarily targets the variability and bilateral coordination characteristics of the walking pattern, which are linked to dynamic walking stability. nGVS might present an effective treatment option to immediately improve walking performance and reduce the incidence of falls in patients with BVP.

Classification of evidence: This study provides Class IV evidence that in patients with BVP, an imperceptible level of nGVS improves dynamic walking stability. *Neurology®* 2016;86:2196–2202

GLOSSARY

BVP = bilateral vestibulopathy; **CV** = coefficient of variation; **cVEMP** = cervical vestibular-evoked myogenic potential; **GVS** = galvanic vestibular stimulation; **nGVS** = noisy galvanic vestibular stimulation; **oVEMP** = ocular vestibular-evoked myogenic potential; **PCI** = phase coordination index; **PWS** = preferred walking speed.

The peripheral vestibular organs sense angular and linear motion of the head to ensure stable gaze and postural balance during self-motion via vestibular-ocular and vestibulospinal reflexes.[1] During locomotion, vestibular feedback essentially contributes to maintenance of dynamic stability by fine-tuning the timing and magnitude of foot displacement.[2–4] Consequently, the gait disorder in patients with bilateral vestibulopathy (BVP) is characterized by increased gait variability and a higher risk of falls.[5,6] Until now, effective treatment options for BVP have been limited to physical therapy.[7,8]

Impaired vestibular information processing due to abnormally elevated vestibular signal detection thresholds is a central consequence of BVP.[9] In the past, signal processing in a variety of sensory systems was shown to be enhanced by adding imperceptible amounts of noise to the system.[10] The rationale behind this phenomenon is a mechanism known as stochastic resonance, where weak undetectable signals can be boosted above the detection threshold by resonating with added white noise.[11] Previous studies used this principle to enhance the sensitivity of residual vestibular afferents in patients with BVP by using galvanic vestibular stimulation

From the German Center for Vertigo and Balance Disorders (M.W., J.D., S.K., A.S., T.B., K.J., R.S.), Department of Neurology (E.N., S.K., A.S., R.S.), and Institute for Clinical Neuroscience (T.B.), University of Munich; and Schoen Klinik Bad Aibling (K.J.), Germany.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

(GVS), a known procedure to electrically stimulate vestibular afferents.[12] Thereby, imperceptible amounts of noisy GVS (nGVS) were shown to improve postural performance in patients with BVP.[13] More recently, it was further demonstrated that nGVS improves walking stability in healthy individuals while walking under visual deprivation[14] and during support surface perturbations.[15]

In the present study, we examined the effects of imperceptible levels of nGVS on walking performance in patients with BVP. We demonstrate that nGVS effectively decreases their walking imbalance and might therefore provide a therapeutic tool to improve walking stability and reduce the incidence of falls in BVP.

METHODS

Level of evidence. The aim of this Class IV evidence study was to examine the effects of imperceptible amounts of nGVS on the walking performance in patients with BVP.

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the ethics committee of the University of Munich and was registered in DRKS (DRKS00007875). All procedures were in accordance with the Helsinki declaration and all patients gave their written informed consent.

Patients. Thirteen patients with BVP (5 women/8 men; mean age 50.1 ± 5.5 years; mean height 1.72 ± 0.03 m; mean weight 74.5 ± 3.1 kg) participated in the study. All patients showed a clinically proven deficit (bilateral pathologic head impulse test and reduced or absent caloric responses, i.e., the sum of maximum slow phase eye velocities during warm and cold caloric irrigation was below 10 deg/s). Cervical vestibular-evoked myogenic potentials (cVEMPs) and ocular VEMPs (oVEMPs) were used as measures of otolith function, i.e., saccular and utricular function, respectively[16] (table 1).

Galvanic vestibular stimulation. GVS was delivered by a battery-driven constant current stimulator (neuroConn, Ilmenau, Germany) via conductive-rubber electrodes, placed in 2 saline-soaked sponges placed over the left and right mastoid process behind the ears. The electrical signal consisted of zero-mean gaussian white noise within a frequency range of 0 to 30 Hz.[13] The intensity of GVS (i.e., peak amplitude) was set to 80% of cutaneous threshold, which was found to be the optimal amplitude for nGVS in patients with BVP.[13] The cutaneous threshold was determined using a stepwise method as described previously.[17] For the nGVS sham condition, the intensity of the nGVS signal was set to 0 μA.

Procedures. Initially, the preferred walking speed (PWS) of each patient was determined during normal overground locomotion on a 6.7-m-long, pressure-sensitive carpet system (GAITRite;

Table 1 Patient characteristics, stimulation amplitudes of nGVS, and effects of nGVS on dynamic walking stability

Patient	Age, y/sex	Etiology	Caloric response, deg/s[a]		Cervical VEMP, μV[b]		Ocular VEMP, μV[c]		nGVS amplitude, μA	Average improvement, %		
			Right	Left	Right	Left	Right	Left		SWS	PWS	FWS
1	24/F	Autoimmune	3	3	27.6	22.5	6.9	5.8	360	53.4	23.9	−16.1
2	71/M	Idiopathic	6	4	0.0	55.0	0.0	15.1	360	9.2	14.2	−14.2
3	41/M	Autoimmune	1	1	0.0	0.0	0.0	0.0	380	16.7	23.1	−3.8
4	43/M	Autoimmune	6	8	0.0	0.0	0.0	0.0	340	9.2	6.4	8.3
5	74/M	Aminoglycoside	9	6	0.0	0.0	0.0	0.0	340	21.8	4.9	−7.4
6	63/M	Idiopathic	3	7	0.0	0.0	0.0	0.0	560	15.6	7.0	25.4
7	66/F	Idiopathic	4	4	97.2	121.3	27.7	20.3	360	18.6	6.6	13.4
8	20/F	Autoimmune	6	6	0.0	0.0	0.0	18.2	100	29.8	17.8	−8.8
9	24/F	Autoimmune	2	4	86.0	88.3	14.8	8.1	280	−20.0	21.3	3.6
10	74/F	Ménière disease	6	5	61.8	102.0	12.7	13.8	360	60.8	−29.6	−6.8
11	45/M	Ménière disease	4	5	52.4	62.2	9.9	7.6	320	31.0	0.8	11.7
12	35/M	Autoimmune	1	4	7.4	11.0	0.0	0.0	640	10.8	8.0	−14.2
13	45/M	Aminoglycoside	4	2	0.0	0.0	0.0	0.0	560	29.6	25.6	12.3
Mean			4.2	4.5	23.4	35.6	5.5	6.9	381.5	22.0	10.0	0.3
SE			0.6	0.5	10.2	12.4	2.4	2.1	38.3	5.2	3.7	3.4

Abbreviations: FWS = fast walking speed; nGVS = noisy galvanic vestibular stimulation; PWS = preferred walking speed; SWS = slow walking speed; VEMP = vestibular-evoked myogenic potential.
Improvements are averaged over all gait measures that showed a response to nGVS, i.e., stride time coefficient of variation (CV), stride length CV, base of support CV, and phase synchronization index.
[a] Sum of maximum slow phase eye velocities during warm and cold caloric irrigation.
[b] Peak-to-peak amplitude between the first positive and negative peaks (p13, n23) that occurred between 13 and 23 milliseconds after stimulus onset.
[c] Amplitude of the first negative peak (n10) that occurred 10 milliseconds after stimulus onset.

CIR Systems, Havertown, PA) with a sampling rate of 120 Hz. Subsequently, steady-state locomotion was measured on a 1.6-m-long, pressure-sensitive treadmill system (Zebris, Isny, Germany; h/p/cosmos, Nussdorf-Traunstein, Germany) with a sampling rate of 100 Hz.

Two different conditions were tested on the treadmill system: (1) walking with zero-amplitude sham nGVS (sham trial), and (2) walking with nonzero-amplitude nGVS (nGVS trial). The 2 conditions were performed in a randomized order and participants were blinded to the stimulation protocol. After completion, participants were asked whether they experienced any change in walking balance (categories: no change, improvement, or deterioration) between the 2 conditions. This procedure was repeated for 3 different walking speeds in a randomized order: PWS, slow walking speed (25% of PWS), and fast walking speed (125% of PWS)—resulting in a total of 6 trials. The recording duration of each trial was 2 minutes. Before each recording, patients were given 1 minute to adapt to the preset treadmill speed. Between trials, they were given at least 3 minutes to recover and to reduce the effect of nGVS, if any, in the preceding trial (figure 1).

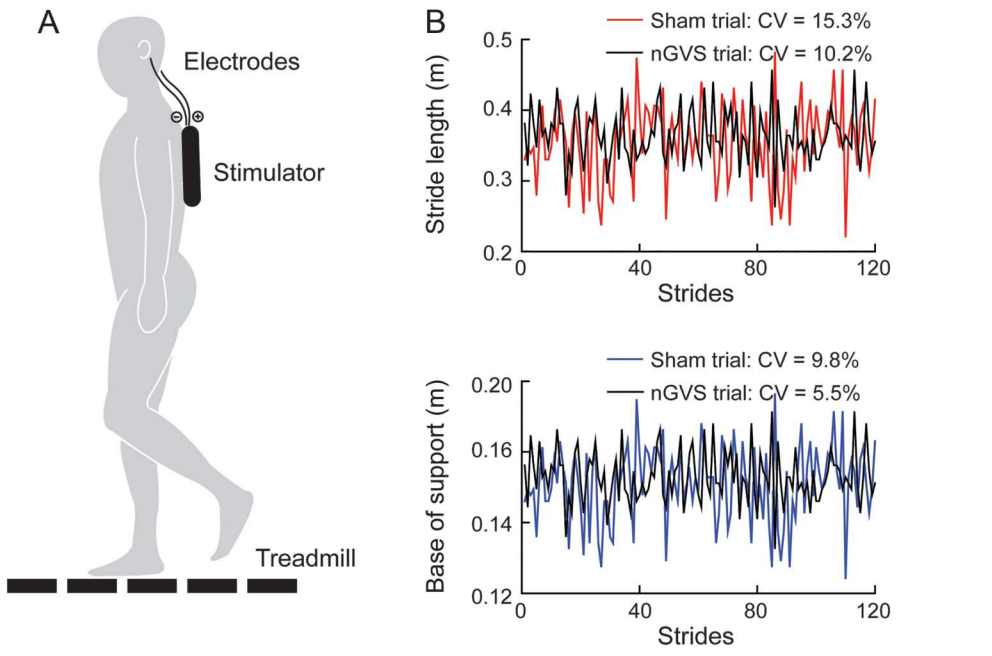
Data analysis. Two different groups of standard gait measures were analyzed. The first group included 4 measures characterizing the mean spatiotemporal gait pattern: stride time, stride length, base of support (i.e., the distance from the heel center of one foot to the line of progression formed by 2 footprints of the opposite foot), and double support time percentage (i.e., the percentage of the total gait cycle duration with both feet being in contact with the ground). The second group included 4 measures quantifying variability of bilateral coordination of walking: the coefficient of variation (CV) of stride time, stride length, and base of support, as well as the bilateral phase synchronization by using the phase coordination index (PCI).[18] The PCI is quantified by first calculating the phase φ_i of the ith heel strike defined as: $\varphi_i = 360^\circ \times \frac{t_{Si}-t_{Li}}{t_{L(i+1)}-t_{Li}}$, where t_{Si} and t_{Li} stand for the time of the ith heel strike of the leg with the short and long mean swing times, respectively, and $t_{L(i+1)} > t_{Si} > t_{Li}$. The PCI is then calculated by: $PCI = 100 \times \frac{\varphi_{ABS}}{180^\circ} + \varphi_{CV}$, where φ_{ABS} is given by: $\varphi_{ABS} = \overline{|\varphi_i - 180^\circ|}$ and φ_{CV} is the CV of the time series φ_i.

Statistical analysis. Data are reported as mean ± SE. The effects of each dependent variable were analyzed using a 2-way repeated-measures analysis of variance and a Bonferroni post hoc analysis with walking speed (slow, preferred, fast) and stimulation condition (sham, nGVS) as factors. Significant interaction effects were further decomposed into simple main effects. The relationship of nGVS effects on walking performance to vestibular function of patients (i.e., caloric response, cVEMP, and oVEMP) as well as their subjective rating of walking balance were analyzed by a Spearman rank correlation. Results were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS (version 20.0; IBM Corp., Armonk, NY).

RESULTS

Walking speeds and nGVS amplitudes. The mean walking speeds examined were 0.2 ± 0.1 m/s for slow walking (range: 0.1–0.4 m/s), 0.8 ± 0.1 m/s for preferred walking (range: 0.3–1.2 m/s), and 1.1 ± 0.1 m/s for fast walking (range: 0.4–1.9 m/s). The mean threshold of sensation for GVS was 475.8 ± 48.2 μA. Accordingly, the mean applied simulation amplitude of nGVS was 381.5 ± 38.3 μA

Figure 1 Experimental setup



(A) Experimental setup: nGVS was delivered by a portable stimulator via electrodes placed on the left and right mastoid process behind the ears. nGVS effects on walking performance of patients with bilateral vestibulopathy were examined on a pressure-sensitive treadmill at 3 speeds (slow, preferred, and fast). (B) Stride length and base of support series of a representative individual while walking slowly during zero-amplitude nGVS (sham trial) and nGVS at an intensity of 560 μA (nGVS trial). During stimulation, CV of stride length improved by 33% and CV of base of support by 43% compared to the sham trial. CV = coefficient of variation; nGVS = noisy galvanic vestibular stimulation.

(corresponding to 80% of the individual cutaneous threshold). None of the patients reported pain or any unpleasant symptoms during or after the nGVS trials (table 1).

nGVS effects on mean spatiotemporal gait measures. None of the examined mean spatiotemporal gait measures such as stride time, stride length, base of support, and double support phase showed any response to nGVS (table 2; figure 2, A–D).

nGVS effects on variability and bilateral coordination gait measures. Compared to the sham trial, walking with nGVS resulted in improvements of all analyzed variability and bilateral coordination gait measures (table 2; figure 2, E–H). Stride time CV decreased by 26.0% ± 8.4% ($p < 0.041$), stride length CV by 26.0% ± 7.7% ($p < 0.029$), base of support CV by 27.8% ± 2.9% ($p < 0.037$), and PCI by 8.4% ± 8.8% ($p < 0.013$). These ameliorating effects of nGVS were predominantly found during slow walking. However, stride length and base of support CV also showed improvements during preferred and fast walking speeds. No correlation was found between the vestibular function of patients (i.e., caloric response, cVEMP, and oVEMP) and nGVS-induced improvements in their walking performance.

nGVS effects on subjective rating of walking balance. The speed-dependent effect of nGVS on objective walking performance was mirrored in the patients' subjective rating of walking balance during the stimulation trials: during slow walking, an improvement in walking balance attributed to nGVS was reported by 6 patients (6: no change; 1: deterioration), for preferred walking by 4 patients (8: no change; 1: deterioration), and for fast walking by only one patient (11: no change; 1: deterioration). A positive correlation between subjective ratings of walking balance and objective improvements in walking performance (averaged over all gait measures that showed a response to nGVS) was found for slow walking (Spearman $\rho = 0.79$, $p < 0.001$) but not for preferred and fast walking.

DISCUSSION We applied imperceptible amounts of nGVS to patients with BVP while walking and provide evidence that nGVS can be effective in improving impaired gait stability of these patients predominantly during slow walking modes. We observed that the ameliorating impact of nGVS is dependent on the walking speed and particularly improves the variability and bilateral coordination characteristics of the walking pattern that are closely linked to dynamic gait stability. The relevance of these results will be discussed regarding (1) the influence of nGVS on the walking performance of patients with BVP, and (2) the presumed mechanism and clinical relevance of nGVS.

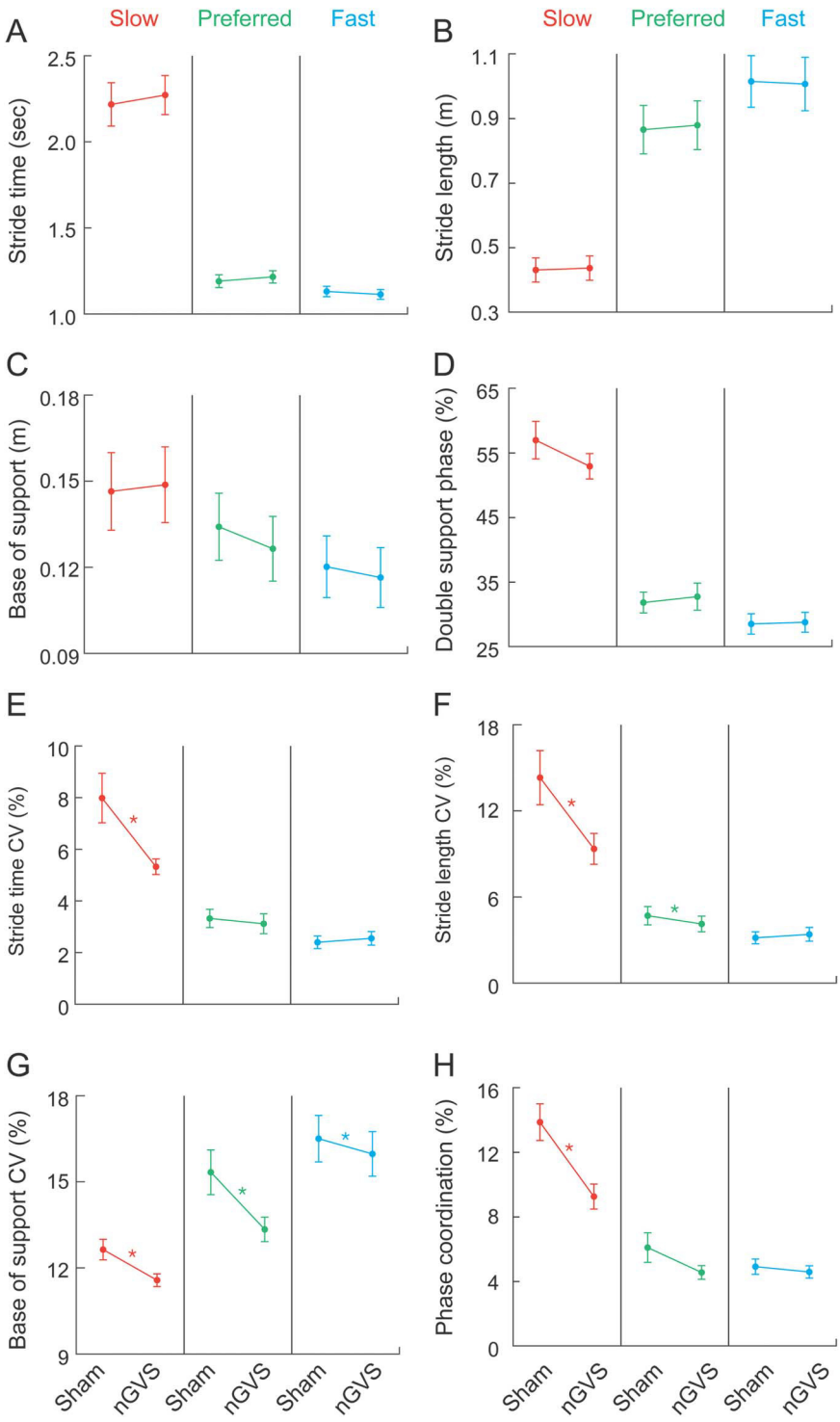
We observed that nGVS primarily influenced the spatiotemporal gait variability and bilateral walking coordination in patients with BVP, in agreement with nGVS effects on walking performance in healthy individuals.[14] Accordingly, nGVS led to decreased stride-to-stride fluctuations in the fore-aft (i.e., stride time and stride length) and mediolateral (i.e., base of support) walking plane as well as a more consistent phase relationship during walking. These gait alterations strongly indicate an enhanced dynamic walking stability.[19–22] Moreover, elevated levels of fore-aft gait variability have been previously shown to be indicative of an increased risk of falls in central and peripheral neurologic gait disorders.[23,24] The observed nGVS-induced improvements of gait variability

Table 2 Repeated-measures analysis of variance results

	Speed (SWS|PWS|FWS)	Condition (sham|nGVS)	Speed × condition
Mean spatiotemporal gait measures			
Stride time	$F_{2,24} = 11.4$, $p < 0.001$[a]	$F_{1,12} = 1.1$, $p = 0.352$	$F_{2,24} = 2.7$, $p = 0.087$
Stride length	$F_{2,24} = 92.9$, $p < 0.001$[a]	$F_{1,12} = 1.0$, $p = 0.346$	$F_{2,24} = 5.4$, $p < 0.013$[a]
Base of support	$F_{2,24} = 9.0$, $p = 0.008$[a]	$F_{1,12} = 1.8$, $p = 0.204$	$F_{2,24} = 2.8$, $p = 0.087$
Double support phase	$F_{2,24} = 150.8$, $p < 0.001$[a]	$F_{1,12} = 3.8$, $p = 0.105$	$F_{2,24} = 1.8$, $p = 0.200$
Variability and bilateral coordination gait measures			
Stride time CV	$F_{2,24} = 50.0$, $p < 0.001$[a]	$F_{1,12} = 8.1$, $p = 0.015$[a]	$F_{2,24} = 5.2$, $p = 0.041$[a]
Stride length CV	$F_{2,24} = 43.4$, $p < 0.001$[a]	$F_{1,12} = 7.6$, $p = 0.017$[a]	$F_{2,24} = 6.1$, $p = 0.029$[a]
Base of support CV	$F_{2,24} = 28.0$, $p < 0.001$[a]	$F_{1,12} = 23.1$, $p < 0.001$[a]	$F_{2,24} = 5.8$, $p = 0.037$[a]
Phase coordination index	$F_{2,24} = 50.1$, $p < 0.001$[a]	$F_{1,12} = 7.1$, $p = 0.021$[a]	$F_{2,24} = 5.7$, $p = 0.013$[a]

Abbreviations: CV = coefficient of variation; FWS = fast walking speed; nGVS = noisy galvanic vestibular stimulation; PWS = preferred walking speed; SWS = slow walking speed.
[a] Significant effect.

Figure 2 nGVS effects on walking performance



Mean ± SE of the 8 examined gait measures (A–D: mean spatiotemporal measures; E–H: variability and bilateral coordination measures) during walking with zero-amplitude nGVS (sham trial) and with nonzero-amplitude nGVS (nGVS trial). nGVS especially improved the variability and bilateral coordination characteristics of the walking pattern and was most effective during slower walking speeds. *Significant change in gait measure between conditions. CV = coefficient of variation; nGVS = noisy galvanic vestibular stimulation.

might therefore also lead to a reduced fall risk in patients with BVP. nGVS-induced improvements in walking performance were further associated with a subjective improvement in walking balance. These observations support the view that vestibular feedback during locomotion is not only required for gaze stabilization and spatial orientation,[25–27] but also essentially contributes to maintenance of dynamic stability

while walking. Accordingly, it has been shown that vestibular feedback influences the walking pattern in a phase-dependent manner by adjusting and smoothing the stride-to-stride walking trajectories in order to compensate for unintended irregularities during motor execution.[2–4] In line with this, we found that noise-enhanced vestibular feedback attributable to nGVS had little to no effect on the mean spatiotemporal gait pattern.

Moreover, we observed that the influence of nGVS on walking performance depended on the walking speed. nGVS improved gait performance primarily during slow walking. This finding is consistent with the growing evidence for a speed-dependent role of sensory feedback in locomotion control. Correspondingly, the impact of a vestibular, visual, or somatosensory loss or perturbation declines with increasing locomotion speed.[5,24,27–29] Thus, active sensory feedback control is thought to be predominantly required for balance control during slow locomotion, whereas internal feedforward commands from central pattern generators in the spinal cord presumably govern balance control at fast locomotion modes.[30] Balance control in the mediolateral walking plane forms an exception of this general picture, since it critically relies on active sensory feedback control independent of locomotion speed.[24,29,31] In line with this, we found that nGVS significantly improved mediolateral gait variability during all examined walking speeds. Although the effects of nGVS on walking performance were primarily observed at speeds below the preferred paces, patients with BVP might especially benefit during phases of slow walking in uncertain or unfamiliar environments (e.g., uneven or slippery grounds, low lighting conditions, navigation in unknown surroundings).

The presumed mechanism underlying the observed effects of nGVS on walking performance in patients with BVP is supposed to be stochastic resonance. According to this mechanism, the ability of a nonlinear system to detect weak signals can be enhanced by addition of a random inference, i.e., white noise.[10,11] By applying this principle to different sensory systems, previous studies could show that the addition of appropriate levels of noise can enhance detection of weak visual, auditory, and tactile stimuli.[32–34] In line with these observations, stochastic resonance is thought to also apply to the vestibular system, since vestibular signal processing is essentially nonlinear.[35] Vestibular information processing in patients with BVP is markedly impaired due to abnormally elevated vestibular signal detection thresholds.[9] Moreover, a considerable amount of vestibular signals during walking from slow to high velocities is even below normal vestibular detection thresholds.[14] In this context, nGVS might be beneficial for patients with BVP who have an intact vestibular nerve contact by enhancing the sensitivity of residual vestibular afferents to facilitate the function of vestibulospinal reflexes required for gait stabilization. These observed effects of nGVS on walking performance in patients with BVP support this assumption. In addition, the observed enhancement of gait performance in patients with BVP might also arise from reduced oscillopsia during walking due to nGVS-induced improvements in vestibulo-ocular reflex gain. Oscillopsia severely impairs visual feedback control during walking with the consequence of increased gait instability.[29,36] In favor of this assumption, there is first evidence for a positive impact of nGVS on ocular-motor function, in particular improved ocular counter-roll reflexes in response to whole-body tilt.[37] However, further studies are required to examine whether nGVS might also improve gaze stabilization during locomotion.

Patients with BVP have oscillopsia and a persistent imbalance during standing and walking that is linked to a higher risk of falls.[6] Impaired walking stability in BVP is further accompanied by an elevated fear of falling with a significant impact on patients' daily mobility and life.[8] The prognosis of BVP is poor in that more than 80% of patients do not show any significant improvements in their condition.[38] Moreover, postural imbalance due to decrements of vestibular function is not limited to disease but also occurs as a cause of aging.[39] Currently, the therapeutic regimen in individuals with bilateral vestibular dysfunction is limited to physical therapy.[7,8] However, approximately half of these individuals do not benefit from this kind of therapeutic approach.[40] The present findings taken together with previous reports on nGVS-induced improvements in static postural balance as well as ocular-motor function in patients with BVP promote nGVS as an alternative therapeutic option for reducing the postural imbalance and incidence of falls in this population.[13,37] However, until now the effects of nGVS in BVP have only been studied during short-term application in a laboratory setting. Future long-term application studies in off-laboratory settings are therefore required to examine the effects of nGVS on daily mobility, incidence of falls, and quality of life in patients with BVP.

AUTHOR CONTRIBUTIONS

M. Wuehr, E. Nusser, T. Brandt, K. Jahn, and R. Schniepp conceptualized and designed the study. M. Wuehr and R. Schniepp drafted the manuscript. M. Wuehr, E. Nusser, and R. Schniepp analyzed and interpreted the data. J. Decker, S. Krafczyk, and A. Straube participated in the acquisition of data. All authors read and approved the final manuscript.

STUDY FUNDING

This work was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG [JA1087/1-1]), the German Hertie Foundation, and the German Federal Ministry of Education and Research (01EO1401).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 21, 2015. Accepted in final form March 4, 2016.

REFERENCES

1. Angelaki DE, Cullen KE. Vestibular system: the many facets of a multimodal sense. Annu Rev Neurosci 2008; 31:125–150.
2. Bent LR. When is vestibular information important during walking?. J Neurophysiol 2004;92:1269–1275.
3. Blouin JS, Dakin CJ, van den Doel K, Chua R, McFadyen BJ, Inglis JT. Extracting phase-dependent human vestibular reflexes during locomotion using both time and frequency correlation approaches. J Appl Physiol 2011;111:1484–1490.
4. Dakin CJ, Inglis JT, Chua R, Blouin JS. Muscle-specific modulation of vestibular reflexes with increased locomotor velocity and cadence. J Neurophysiol 2013;110:86–94.
5. Schniepp R, Wuehr M, Neuhaeusser M, et al. Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure. Mov Disord 2011;27:125–131.
6. Herdman SJ, Blatt P, Schubert MC, Tusa RJ. Falls in patients with vestibular deficits. Am J Otol 2000;21:847–851.
7. Zingler VC, Cnyrim C, Jahn K, et al. Causative factors and epidemiology of bilateral vestibulopathy in 255 patients. Ann Neurol 2007;61:524–532.
8. Guinand N, Boselie F, Guyot JP, Kingma H. Quality of life of patients with bilateral vestibulopathy. Ann Otol Rhinol Laryngol 2012;121:471–477.
9. Priesol AJ, Valko Y, Merfeld DM, Lewis RF. Motion perception in patients with idiopathic bilateral vestibular hypofunction. Otolaryngol Head Neck Surg 2014;150:1040–1042.
10. Moss F. Stochastic resonance and sensory information processing: a tutorial and review of application. Clin Neurophysiol 2004;115:267–281.
11. Collins JJ, Chow CC, Imhoff TT. Stochastic resonance without tuning. Nature 1995;376:236–238.
12. Fitzpatrick RC. Probing the human vestibular system with galvanic stimulation. J Appl Physiol 2004;96:2301–2316.
13. Iwasaki S, Yamamoto Y, Togo F, et al. Noisy vestibular stimulation improves body balance in bilateral vestibulopathy. Neurology 2014;82:969–975.
14. Wuehr M, Nusser E, Krafczyk S, et al. Noise-enhanced vestibular input improves dynamic walking stability in healthy subjects. Brain Stim 2015;9:109–116. DOI: 10.1016/j.brs.2015.08.017.
15. Mulavara AP, Kofman IS, De Dios YE, et al. Using low levels of stochastic vestibular stimulation to improve locomotor stability. Front Syst Neurosci 2015:9:117.
16. Agrawal Y, Bremova T, Kremmyda O, Strupp M. Semicircular canal, saccular and utricular function in patients with bilateral vestibulopathy: analysis based on etiology. J Neurol 2012;260:876–883.
17. Wilkinson D, Nicholls S, Pattenden C, Kilduff P, Milberg W. Galvanic vestibular stimulation speeds visual memory recall. Exp Brain Res 2008;189:243–248.
18. Plotnik M, Giladi N, Hausdorff JM. A new measure for quantifying the bilateral coordination of human gait: effects of aging and Parkinson's disease. Exp Brain Res 2007; 181:561–570.
19. Hausdorff JM. Gait variability: methods, modeling and meaning. J Neuroeng Rehabil 2005;2:19.
20. Brach JS, Berlin JE, VanSwearingen JM, Newman AB, Studenski SA. Too much or too little step width variability is associated with a fall history in older persons who walk at or near normal gait speed. J Neuroeng Rehabil 2005;2:2–21.
21. Krasovsky T, Banina MC, Hacmon R, Feldman AG, Lamontagne A, Levin MF. Stability of gait and interlimb coordination in older adults. J Neurophysiol 2012;107: 2560–2569.
22. Wuehr M, Pradhan C, Brandt T, Jahn K, Schniepp R. Patterns of optimization in single- and inter-leg gait dynamics. Gait Posture 2014;39:733–738.
23. Schniepp R, Wuehr M, Schlick C, et al. Increased gait variability is associated with the history of falls in patients with cerebellar ataxia. J Neurol 2013;261:213–223.
24. Wuehr M, Schniepp R, Schlick C, et al. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. Gait Posture 2014;39:852–858.
25. Pozzo T, Berthoz A, Lefort L, Vitte E. Head stabilization during various locomotor tasks in humans. Exp Brain Res 1991;85:208–217.
26. Fitzpatrick RC, Wardman DL, Taylor JL. Effects of galvanic vestibular stimulation during human walking. J Physiol 2004;517:931–939.
27. Jahn K, Strupp M, Schneider E, Dieterich M, Brandt T. Differential effects of vestibular stimulation on walking and running. Neuroreport 2000;11:1745–1748.
28. Brandt T, Strupp M, Benson J. You are better off running than walking with acute vestibulopathy. Lancet 1999;354:746.
29. Wuehr M, Schniepp R, Pradhan C, et al. Differential effects of absent visual feedback control on gait variability during different locomotion speeds. Exp Brain Res 2012; 224:287–294.
30. Lambert FM, Combes D, Simmers J, Straka H. Gaze stabilization by efference copy signaling without sensory feedback during vertebrate locomotion. Curr Biol 2012; 22:1649–1658.
31. Bauby CE, Kuo AD. Active control of lateral balance in human walking. J Biomech 2000;33:1433–1440.
32. Riani M, Simonotto E. Stochastic resonance in the perceptual interpretation of ambiguous figures: a neural network model. Phys Rev Lett 1994;72:3120–3123.
33. Zeng FG, Fu QJ, Morse R. Human hearing enhanced by noise. Brain Res 2000;869:251–255.
34. Collins JJ, Imhoff TT, Grigg P. Noise enhanced information transmission in rat SA1 cutaneous mechanoreceptors via aperiodic stochastic resonance. J Neurophysiol 1996; 76:642–645.
35. Sadeghi SG, Chacron MJ, Taylor MC, Cullen KE. Neural variability, detection thresholds, and information transmission in the vestibular system. J Neurosci 2007;27:771–781.
36. Bronstein AM. Vision and vertigo: some visual aspects of vestibular disorders. J Neurol 2004;251:381–387.
37. Serrador JM, Geraghty MC, Deegan BM, Wood SJ. Enhancing vestibular function by imperceptible electrical stimulation. J Vestib Res 2011;21:101–103. Abstract.
38. Zingler VC, Weintz E, Jahn K, et al. Follow-up of vestibular function in bilateral vestibulopathy. J Neurol Neurosurg Psychiatry 2008;79:284–288.
39. Serrador JM, Lipsitz LA, Gopalakrishnan GS, Black FO, Wood SJ. Loss of otolith function with age is associated with increased postural sway measures. Neurosci Lett 2009;465:10–15.
40. Gillespie MB, Minor LB. Prognosis in bilateral vestibular hypofunction. Laryngoscope 1999;109:35–41.

8. Zusammenfassung

Patienten mit einer bilateralen Vestibulopathie (BVP) leiden aufgrund fehlender vestibulookulärer und vestibulospinaler Reflexfunktionen unter Stand- und Gangunsicherheit, bewegungsabhängigem Schwindel, Oszillopsien mit unscharfem Sehen bei Kopfbewegungen und unter räumlichen Orientierungsstörungen (Zingler, Weintz et al. 2009). Die Patienten sind in Ihrem Alltag stark eingeschränkt und haben ein deutlich erhöhtes Sturzrisiko (Schlick, Schniepp et al. 2016). Die Standardbehandlung ist ein physiotherapeutisches Gleichgewichtstraining. Auf diese Behandlung spricht nur etwa die Hälfte der Patienten an mit meist nur moderatem Therapieeffekt (Gillespie and Minor 1999).

Für die vorliegende Dissertation wurde ein alternativer Therapieansatz für Patienten mit BVP untersucht. Der Behandlungsansatz basiert auf dem Phänomen der stochastischen Resonanz, demzufolge sich die Signalverarbeitung von sensorischen Systemen durch die Beigabe eines schwachen Rauschsignals verbessern lässt. In einer vorangegangen Studie konnte bereits gezeigt werden, dass sich mit Hilfe einer nicht wahrnehmbaren galvanischen vestibulären Rauschstimulation die statische Haltungsstabilität bei Patienten mit BVP verbessern lässt (Iwasaki, Yamamoto et al. 2014). Darauf aufbauend wurde nun der Einfluss der vestibulären Rauschstimulation auf die dynamische Gangstabilisierung bei gesunden Probanden sowie bei Patienten mit BVP untersucht. Es zeigte sich, dass die vestibuläre Rauschstimulation bei Gesunden und insbesondere bei Patienten zu einer effektiven, objektiv messbaren sowie subjektiv empfundenen Stabilisierung des Gangverhaltens führt. Die Stimulation verringerte die spatiotemporale Gangvariabilität, die bei Patienten ein Indikator für ein erhöhtes Risiko zu stürzen darstellt. Zudem war der Einfluss der Stimulation vornehmlich während des langsamen Gehens zu beobachten, das bei Patienten am stärksten durch den vestibulären Funktionsausfall beeinträchtigt ist.

Eine schwache Rauschreizung des vestibulären Systems führt also bei Patienten mit BVP zu einer effektiven Stabilisierung des statischen und dynamischen Gleichgewichts. Damit stellt diese Stimulation einen nicht invasiven vielversprechenden Therapieansatz für Patienten mit BVP dar.

9. Summary

Impaired vestibulo-ocular and vestibulo-spinal reflex functions in patients with bilateral vestibulopathy (BVP) result in standing and walking insecurity as well as disturbed gaze stabilization during head movements and compromised spatial orientation (Zingler, Weintz et al. 2009). These disabilities not only impact patients' daily activities and quality of life but are also linked to an increased risk of falling (Schlick, Schniepp et al. 2016). The standard therapeutic approach for BVP is a physical balance training. However, only about half of the patients respond to the treatment with mostly only a moderate therapeutic effect (Gillespie and Minor 1999).

The aim of the present thesis was to pursue an alternative therapeutic approach for patients with BVP. This treatment approach is based on the phenomenon of stochastic resonance, by which signal processing in sensory systems can be improved in the presence of a concomitant weak sensory noise stimulation. In a previous study it was already shown that an imperceptible noisy galvanic vestibular stimulation can effectively improve static stability of posture in patients with BVP (Iwasaki, Yamamoto et al. 2014).

Based on this finding, we have investigated the influence of an imperceptible noisy vestibular stimulation on dynamic gait stabilization in healthy subjects and in patients with BVP. We found that vestibular noise stimulation leads to an effective, objectively measurable and subjectively perceived stabilization of the gait behavior in healthy subjects and especially in patients. Improvements in gait performance were in particular linked to a reduced amount of spatio-temporal gait variability, which is an indicator of an increased risk of falling in patients with BVP. In addition, the influence of the imperceptible noise stimulation was observed mainly during slow walking, i.e. the walking mode which is mostly affected by vestibular dysfunction in patients.

The findings of this thesis demonstrate that a weak noisy stimulation of the vestibular system in patients with BVP leads to an effective stabilization of their static and dynamic balance capabilities. Thus, this new stimulation technique represents a promising non-invasive treatment approach for patients with BVP.

10. Literaturverzeichnis

Brandt, D. M., Strupp M. (2012). Leitsymptom Schwindel. Heidelber, Springer Medizin.

Brandt, T., SchautzerF., D. A. Hamilton, R. Bruning, H. J. Markowitsch, R. Kalla, C. Darlington, P. Smith and M. Strupp (2005). "Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans." Brain **128**(Pt 11): 2732-2741.

Brandt, T., M. Strupp and J. Benson (1999). "You are better off running than walking with acute vestibulopathy." Lancet **354**(9180): 746.

Gandevia, S. C., D. I. McCloskey and D. Burke (1992). "Kinaesthetic signals and muscle contraction." Trends Neurosci **15**(2): 62-65.

Gillespie, M. B. and L. B. Minor (1999). "Prognosis in bilateral vestibular hypofunction." Laryngoscope **109**(1): 35-41.

Gray, O. (1955). "A brief survey of the Phylogenesis of the labyrinth. " Laryngol Otol 69: 151-179.

Herdman, S. J., C. D. Hall, M. C. Schubert, V. E. Das and R. J. Tusa (2007). "Recovery of dynamic visual acuity in bilateral vestibular hypofunction." Arch Otolaryngol Head Neck Surg **133**(4): 383-389.

Horak, F. B., C. L. Shupert, V. Dietz and G. Horstmann (1994). "Vestibular and somatosensory contributions to responses to head and body displacements in stance." Exp Brain Res **100**(1): 93-106.

Iwasaki, S., Y. Yamamoto, F. Togo, M. Kinoshita, Y. Yoshifuji, C. Fujimoto and T. Yamasoba (2014). "Noisy vestibular stimulation improves body balance in bilateral vestibulopathy." Neurology **82**(11): 969-975.

Jahn, K., A. Deutschlander, T. Stephan, M. Strupp, M. Wiesmann and T. Brandt (2004). "Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging." Neuroimage **22**(4): 1722-1731.

Jahn, K., M. Strupp, E. Schneider, M. Dieterich and T. Brandt (2000). "Differential effects of vestibular stimulation on walking and running." Neuroreport **11**(8): 1745-1748.

Jaramillo, F. and K. Wiesenfeld (1998). "Mechanoelectrical transduction assisted by Brownian motion: a role for noise in the auditory system." Nat Neurosci **1**(5): 384-388.

Keywan, A., M. Wuehr, C. Pradhan and K. Jahn (2018). "Noisy Galvanic Stimulation Improves Roll-Tilt Vestibular Perception in Healthy Subjects." Front Neurol **9**: 83.

Krebs, D. E., K. M. Gill-Body, P. O. Riley and S. W. Parker (1993). "Double-blind, placebo-controlled trial of rehabilitation for bilateral vestibular hypofunction: preliminary report." Otolaryngol Head Neck Surg **109**(4): 735-741.

Moss, F., L. M. Ward and W. G. Sannita (2004). "Stochastic resonance and sensory information processing: a tutorial and review of application." Clin Neurophysiol **115**(2): 267-281.

Mulavara, A. P., M. J. Fiedler, I. S. Kofman, S. J. Wood, J. M. Serrador, B. Peters, H. S. Cohen, M. F. Reschke and J. J. Bloomberg (2011). "Improving balance function using vestibular stochastic resonance: optimizing stimulus characteristics." Exp Brain Res **210**(2): 303-312.

Nashner, L. M. (1980). "Balance adjustments of humans perturbed while walking." J Neurophysiol **44**(4): 650-664.

Priplata, A. A., J. B. Niemi, J. D. Harry, L. A. Lipsitz and J. J. Collins (2003). "Vibrating insoles and balance control in elderly people." Lancet **362**(9390): 1123-1124.

Schlick, C., R. Schniepp, V. Loidl, M. Wuehr, K. Hesselbarth and K. Jahn (2016). "Falls and fear of falling in vertigo and balance disorders: A controlled cross-sectional study." J Vestib Res **25**(5-6): 241-251.

Schniepp, R., M. Wuehr, M. Neuhaeusser, M. Kamenova, K. Dimitriadis, T. Klopstock, M. Strupp, T. Brandt and K. Jahn (2012). "Locomotion speed determines gait variability in cerebellar ataxia and vestibular failure." Mov Disord **27**(1): 125-131.

Serrador, J. M., B. M. Deegan, M. C. Geraghty and S. J. Wood (2018). "Enhancing vestibular function in the elderly with imperceptible electrical stimulation." Sci Rep **8**(1): 336.

Trepel, M. (1999). Neuroanatomie, Struktur und Funktion. München, Stuttgart, Jena, Lübeck, Ulm, Urban & Fischer.

Wuehr, M., J. C. Boerner, C. Pradhan, J. Decker, K. Jahn, T. Brandt and R. Schniepp (2018). "Stochastic resonance in the human vestibular system - Noise-induced facilitation of vestibulospinal reflexes." Brain Stimul **11**(2): 261-263.

Wuehr, M., R. Schniepp, C. Schlick, S. Huth, C. Pradhan, M. Dieterich, T. Brandt and K. Jahn (2014). "Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy." Gait Posture **39**(3): 852-858.

Zingler, V. C., E. Weintz, K. Jahn, D. Huppert, C. Cnyrim, T. Brandt and M. Strupp (2009). "Causative factors, epidemiology, and follow-up of bilateral vestibulopathy." Ann N Y Acad Sci **1164**: 505-508.

Zingler, V. C., E. Weintz, K. Jahn, A. Mike, D. Huppert, N. Rettinger, T. Brandt and M. Strupp (2008). "Follow-up of vestibular function in bilateral vestibulopathy." J Neurol Neurosurg Psychiatry **79**(3): 284-288.

11. Danksagung

Zuerst möchte ich mich bei Herrn Prof. Dr. Klaus Jahn für die Bereitstellung dieses interessanten Themas sowie die kompetente und sehr zuverlässige Betreuung als Doktorvater bedanken.

Außerdem bedanke ich mich ganz herzlich bei Herrn Dr Max Wühr, der an der Entstehung der Arbeit maßgeblich beteiligt war und der mir stets mit kompetenten Ratschlägen und aufmunternden Worten zur Seite stand. Die Betreuung hätte besser nicht sein können.

Ein großer Dank für die intensive Unterstützung gilt außerdem allen Mitarbeitern der neurologischen Klinik, welche mich bei meinem Projekt unterstützt haben, insbesondere Julian Decker, Dr. Roman Schniepp, Dr. Siegbert Krafczyk, Prof. Dr. Andreas Straube und Prof. Dr. Dr. Thomas Brandt.

Ein ganz besonderer Dank gilt auch allen Teilnehmern der Studien. Sie haben für die Untersuchungen viel Zeit zur Verfügung gestellt.

Zum Schluss möchte ich noch meiner Familie und meinen Freunden danken, die in den Jahren der Entstehung dieser Arbeit Teil meines Lebens waren und mich unterstützt haben.

12. Eigenanteil an den vorgelegten Arbeiten

Der wissenschaftliche Fokus der vorliegenden Dissertation „Einfluss einer galvanischen vestibulären Rauschstimulation auf die Gangstabilität bei gesunden Probanden und bei Patienten mit bilateraler Vestibulopathie“ hat sich nach Durchsicht der gegenwärtigen Literatur, insbesondere einer vorangegangenen Studie von Iwasaki, Yamamoto et al. 2014, welche eine verbesserte statische Haltungsstabilität bei Patienten mit BVP durch nicht wahrnehmbare galvanische vestibuläre Rauschstimulation zeigte, im gemeinsamen Dialog mit Herrn Prof. Klaus Jahn, Dr. Max Wühr, Dr. Roman Schniepp und mir ergeben, woraufhin die Forschungsfragen der beiden Studien gemeinschaftlich formuliert und das Studiendesign konzipiert wurden.

Nach Festlegung der Einschlusskriterien erfolgte die Probanden- und Patientenrekrutierung durch meine Person.

Die Datenerhebung beider Studien führte ich selbständig mit Unterstützung durch meinen Betreuer Dr. Max Wühr und Julian Decker durch. Bei speziellen Fragestellungen standen zusätzlich Dr. Kraftzyk und Prof. Dr. Straube unterstützend zur Verfügung.

Die Datenanalyse und -Auswertung beider Studien führte ich eiegnständig in Rücksprache mit Dr. Max Wühr und Dr. Roman Schniepp durch.

Der erste Manuskriptentwurf der 1. Veröffentlichung „Noise-Enhanced Vestibular Input Improves Dynamic Walking Stability in Healthy Subjects“ wurde von mir im Dialog mit Dr. Roman Schniepp und Dr. Max Wühr verfasst.

Der erste Manuskriptentwurf der 2. Veröffentlichung „Noisy vestibular stimulation improves dynamic walking stability in bilateral vestibulopathy“ entstand in enger Zusammenarbeit mit mir durch Dr. Max Wühr und Dr. Roman Schniepp.

Die jeweiligen Review-Verfahren wurden in Rücksprache mit den Koautoren selbstständig durchgeführt und von den Reviewern gewünschte Änderungen an den Manuskripten vorgenommen.