Aus dem Deutschen Schwindel- und Gleichgewichtszentrum (DSGZ)

Klinikum der Ludwig-Maximilians-Universität München

Anwendung von Galvanischer Vestibulärer Stimulation zur Behandlung der Bilateralen Vestibulopathie

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität München

vorgelegt von

Josefine Leonie Eder

aus

Trostberg

Jahr

2025

Mit Genehmigung der Medizinischen Fakultät

der Ludwig-Maximilians-Universität München

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Inhaltsverzeichnis

Abkürzungsverzeichnis

BVP	Bilaterale Vestibulopathie
GVS	Galvanische vestibuläre Stimulation
nGVS	noisy GVS – vestibuläre Rauschstimulation
Patienten	Patienten jeglicher geschlechtlichen Zuordnung
vHIT	Video Head-Impulse-Test
VOR	Vestibulo-okulärer Reflex
VRT	Vestibuläre Rehabilitationstherapie

Publikationsliste

Paper I

Combining vestibular rehabilitation with noisy galvanic vestibular stimulation for treatment of bilateral vestibulopathy

Josefine Eder, Silvy Kellerer, Tamara Amberger, Aram Keywan, Julia Dlugaiczyk, Max Wuehr, Klaus Jahn

Journal of Neurology (2022) 269:5731–5737

doi: 10.1007/s00415-022-11033-x

Paper II

Noisy galvanic vestibular stimulation improves vestibular perception in bilateral vestibulopathy

Max Wuehr, Josefine Eder, Aram Keywan, Klaus Jahn

Journal of Neurology (2023) 270:938-943

doi: 10.1007/s00415-022-11438-8

Zusätzlich:

Paper III (Anhang)

Mechanisms underlying treatment effects of vestibular noise stimulation on postural instability in patients with bilateral vestibulopathy

Max Wuehr, Josefine Eder, Silvy Kellerer, Tamara Amberger, Klaus Jahn

Journal of Neurology (2024) 271:1408-1415

doi: 10.1007/s00415-023-12085-3

1. Beitrag zu den Veröffentlichungen

1.1. Beitrag zu Paper I

Das Studiendesign für die Arbeit „Combining vestibular rehabilitation with noisy galvanic vestibular stimulation for treatment of bilateral vestibulopathy“ wurde von Herrn Prof. Dr. med. Klaus Jahn, Frau Prof. Dr. med. Julia Dlugaizcyk und Herrn PD Dr. rer. nat. Max Wühr entworfen. Die Rekrutierung und Betreuung der Patienten, sowie die Datenerhebung erfolgte im ersten Teil durch Tamara Amberger und anschließend durch mich. Silvy Kellerer führte als erfahrene Schwindelphysiotherapeutin das vestibuläre Rehabilitationstraining durch. Die Datenanalyse und -auswertung führte ich selbstständig in Rücksprache mit Herrn PD Dr. rer. nat. Max Wühr und Herrn Prof. Dr. med. Klaus Jahn durch. Das Manuskript für die Veröffentlichung wurde von mir in Absprache mit Herrn Prof. Dr. med. Klaus Jahn und Herrn PD Dr. rer. nat. Max Wühr verfasst.

1.2. Beitrag zu Paper II

Das Studiendesign für den Artikel „Noisy galvanic vestibular stimulation improves vestibular perception in bilateral vestibulopathy“ wurde von Herrn Prof. Dr. med. Klaus Jahn und Herrn PD Dr. rer. nat. Max Wühr erstellt. Nach Definition der Einschlusskriterien wurden die Patienten und Probanden durch mich rekrutiert und betreut. Die Datenerhebung führte ich eigenständig durch. In Rücksprache mit Herrn Prof. Dr. med. Klaus Jahn und Herrn PD Dr. rer. nat. Max Wühr wurden die Daten durch meine Person analysiert und ausgewertet. Die Matlab-spezifischen Daten wertete freundlicherweise Herr Dr. Aram Keywan aus. Das Manuskript für die Veröffentlichung wurde durch Herrn PD Dr. rer. nat. Max Wühr in enger Rücksprache mit mir verfasst.

1.3. Beitrag zu Paper III (Anhang)

Die Studie für das Paper „Mechanisms underlying treatment effects of vestibular noise stimulation on postural instability in patients with bilateral vestibulopathy“ wurde von Herrn Prof. Dr. med. Klaus Jahn und Herrn PD Dr. rer. nat. Max Wühr entworfen. Die Rekrutierung nach den definierten Einschlusskriterien, die Betreuung der Patienten, sowie die Datenerhebung erfolgte im ersten Teil durch Tamara Amberger und anschließend durch mich. Die Datenanalyse und -auswertung, sowie die Verfassung des Manuskripts für die Veröffentlichung erfolgte durch Herrn PD Dr. rer. nat. Max Wühr in Rücksprache mit Herrn Prof. Dr. med. Klaus Jahn und mir.

2. Einleitung

Das Halten der Balance erfordert ein komplexes Zusammenspiel aus eingehenden vestibulären, visuellen und propriozeptiven Informationen, die im Gehirn verarbeitet und zu einer präzisen posturalen Reaktion als Antwort darauf umgesetzt werden. Bei Patienten, die an einer Bilateralen Vestibulopathie (BVP) leiden, ist das Gleichgewichtsorgan beidseitig ausgefallen, wodurch der vestibuläre Anteil als einer der drei wichtigsten Faktoren für den Erhalt der Körperstabilität verloren geht.

Um diesen Patienten zu helfen ihr Gleichgewicht wieder zu finden, empfiehlt man derzeit ein vestibuläres Rehabilitationstraining, bei welchem durch spezielle physiotherapeutische Übungen die Balance trainiert wird (1).

Da diese Therapie nicht immer den erhofften großen Effekt erzielt, arbeitet die aktuelle Forschung an alternativen und ergänzenden Ansätzen. Ein vielversprechendes Projekt ist der Einsatz von galvanischer vestibulärer Rauschstimulation (nGVS), wodurch bereits in mehreren vorangegangenen Studien sowohl bei Gesunden als auch bei Erkrankten positive Effekte auf die Stand- und Gangstabilität nachgewiesen werden konnten (2-5).

Dabei nutzt man das Prinzip der stochastischen Resonanz, wodurch bei einer unterschwelligen elektrischen Stimulation mit einem Rauschreiz die Wahrnehmungsschwelle neurologischer Systeme herabgesetzt und so die Informationsverarbeitung verbessert werden kann (6). Für das Gleichgewichtssystem konnte dieser Optimierungseffekt durch die Herabsetzung der Wahrnehmungsschwelle kleinster Bewegungen nachgewiesen werden (7).

Das vorliegende Forschungsprojekt kombiniert in der ersten Studie (8) die bewährte Therapiemethode der vestibulären Physiotherapie mit dem neuen Therapieansatz der nGVS. Die zweite Studie (9) testet den Effekt der nGVS auf die Gleichgewichtswahrnehmung im Sitzen bei BVP-Patienten.

2.1. Bilaterale Vestibulopathie

Schwindel und Gleichgewichtsstörungen schränken Betroffene in ihrem Lebensalltag ein. Die jährliche Prävalenz für Schwindelerkrankungen im Allgemeinen liegt bei bis zu 20% der Erwachsenen (10). Dabei sind besonders chronische Formen des Schwindels belastend für die Patienten. Eine spezielle Erkrankung ist die Bilaterale Vestibulopathie, bei der aus unterschiedlichen Gründen ein kompletter oder inkompletter Funktionsverlust beider Gleichgewichtsorgane vorliegt. Schätzungen haben ergeben, dass in Europa und den USA zusammen ca. 53-95 Millionen Menschen an dieser Schwindelerkrankung leiden (11).

2.1.1. Ätiologie und Symptomatik

Die häufigsten Ursachen für den peripheren Ausfall der Vestibularorgane sind die Einnahme ototoxischer Medikamente (13%), ein beidseitiger Morbus Menière (7%), entzündliche Erkrankungen (z. B. Enzephalitis, Meningitis), Autoimmunerkrankungen, degenerative Erkrankungen oder Tumore (z.B. beidseitiges Akustikusneurinom) (12). Bei etwa der Hälfte der Fälle bleibt die Ätiologie jedoch trotz gründlicher Ursachensuche ungeklärt (12).

Typischerweise äußert sich die verminderte vestibuläre Funktion durch einen bewegungsabhängigen Schwankschwindel, chronisches Ungleichgewicht und posturale Instabilität während des Stehens und Gehens. Vor allem in der Dämmerung oder im Dunkeln und auf unebenem Untergrund sind die Symptome deutlich stärker ausgeprägt. Außerdem leiden viele Patienten an Oszillopsien, das heißt, dass die Umwelt bei Bewegung als verwackelt wahrgenommen wird und die Blickstabilisierung erschwert ist. Hierdurch wird die gesamte Schwindelproblematik nochmals verstärkt (13). Das Gangbild der Betroffenen ist auffällig und lässt sich durch einen breitbasigen, unsicheren Gang charakterisieren, der sich bei Geschwindigkeitssteigerung oder kognitiver Ablenkung bessert (14).

Diese Beeinträchtigungen führen dazu, dass viele Betroffene eine niedrigere Lebensqualität angeben und verglichen mit dem Leben vor Krankheitsbeginn subjektiv mehr Alltagseinschränkungen empfinden. Das Sturzrisiko ist im Vergleich zur Normalbevölkerung vierfach erhöht (15).

2.1.2. Diagnostik und Therapie

Zusätzlich zur Anamnese kann in der Diagnostik die Funktion des vestibulo-okulären Reflexes (VOR) geprüft werden. Dies geschieht für die niedrigen Frequenzen durch eine kalorische Ohrspülung, bei der getestet wird, ob das Gleichgewichtsorgan regelrecht auf Warm- und Kaltwasserspülung reagiert. Außerdem wird beim video-Head-Impulse-Test (vHIT) der VOR für höhere Frequenzen getestet. Ist in der kalorischen Ohrspülung die Summe der Geschwindigkeit der langsamen Nystagmusphase (slow phase velocity) für Kalt- und Warmspülung auf beiden Seiten auf <6°/sek reduziert und/oder der Verstärkungsfaktor des VOR im vHIT mit einem Wert <0,6 pathologisch und sind gleichzeitig die typischen Symptome der Krankheit vorhanden, kann man von einer Bilateralen Vestibulopathie sprechen (13).

Die einzige Therapiemöglichkeit, die BVP-Patienten derzeit zu Verfügung steht, ist die regelmäßige vestibuläre Rehabilitationstherapie, die die Balance der Patienten trainieren soll (1). Der Fokus wird hierbei auf das visuelle und das propriozeptive System gelegt, denn diese sind beim gesunden Menschen zusammen mit der Gleichgewichtswahrnehmung für die Stabilität des Körpers in Ruhe und Bewegung verantwortlich. Da bei BVP-Patienten das Gleichgewichtsorgan keine brauchbaren Informationen liefert, müssen die beiden anderen Systeme gut trainiert werden, sodass der Ausfall kompensiert werden kann. Die Grundelemente des Trainings sind Blickstabilisierungsübungen und Übungen zur Augen-Kopf-Koordination während des Stehens und Gehens (16). Um den Schwierigkeitsgrad an die individuellen Voraussetzungen und Probleme jedes einzelnen Patienten anzupassen, können die Übungen wahlweise mit geschlossenen Augen, auf Schaumstoff oder in Kombination miteinander ausgeführt werden. Die Effekte des vestibulären Trainings gehen jedoch nicht über eine partielle Kompensation der Gleichgewichtsstörung hinaus (17). Außerdem sind die Langzeiteffekte dieser Intervention nicht sehr erfolgsversprechend (18).

Die Forschung beschäftigt sich deshalb derzeit mit mehreren anderen Therapieansätzen, wie beispielsweise einem vestibulären Implantat in das Gleichgewichtsorgan, das den Gleichgewichtsnerven gezielt stimulieren soll. Das Implantat wurde bereits im Tierversuch und an einzelnen Patienten getestet und hat dabei vielversprechende Ergebnisse geliefert (19). Die operative Implantation geht jedoch durch die anatomische Nähe zum Gehörorgan mit einem hohen Risiko einer Beschädigung der Hörfunktion einher.

Eine nicht-invasive Alternative stellt die Neurostimulationsmethode der Galvanischen Vestibulären Stimulation (GVS) dar (20). Da diese Inhalt der beiden hier vorgelegten Studien ist, wird im Folgenden genauer auf die Methode eingegangen.

2.2. Galvanische Vestibuläre Stimulation

Bei der Galvanischen Stimulation handelt es sich um eine Methode, die schon viele Jahre bekannt ist und erforscht wird. Als Erstbeschreiber und Namensgeber gilt Luigi Galvani, der 1791 elektrischen Strom in Form von Blitzen an Froschschenkel anlegte und feststellte, dass dadurch eine Muskelkontraktion erfolgt (21). Mittlerweile wurde die Methode der elektrischen Stimulation weiterentwickelt und findet heute auf verschiedenste Weisen Anwendung in der neurologischen Forschung (22). In Bezug auf das Gleichgewichtsorgan spricht man dabei von der Galvanischen Vestibulären Stimulation (GVS). Hier wird die GVS in Form von Impulsen (23), Stufen (24) oder als Sinusstimulation (25) mit elektrischen Reizen über der Wahrnehmungsschwelle eingesetzt. Der überschwellige Reiz führt zu einer direkten Stimulation des Gleichgewichtsnerven, was im Gehirn den Eindruck einer Kopfbewegung simuliert, worauf der Körper mit einer komplexen Antwort in Form eines Balanceausgleichs reagiert (26). Eine besondere Form der GVS ist die galvanische Rauschstimulation, oder noisy GVS (nGVS), die mit Reizen eines Rauschspektrums unter der Wahrnehmungsschwelle arbeitet. Der Nerv wird also nicht direkt stimuliert, sondern indirekt angeregt, wodurch die Sensitivität für externe Reize erhöht wird (20). Damit konnte man unter anderem positive Effekte sowohl auf die Körperbalance (27), als auch in den Bereichen der visuellen (28), auditiven (29) und taktilen Wahrnehmung (30) nachweisen.

Als Erklärung für die nGVS dient das Phänomen der stochastischen Resonanz, das in Abbildung 1 schematisch dargestellt ist. Es funktioniert in einem nicht-linearen neuronalen System, wie beispielsweise dem Gleichgewichtssystem oder dem Gehör. In einem solchen System werden Informationen nur dann weitergeleitet, wenn sie einen gewissen Schwellenwert (Detection Threshold) überschreiten. Ist das Signal zu schwach, wird der Schwellenwert nicht überschritten und es gelangt keine Information ins Gehirn (Sub-threshold Signal). Wird diesem System

nun ein unterschwellig schwacher, rauschender elektrischer Reiz in Form der galvanischen Rauschstimulation (nGVS) zugefügt, überlagert sich das galvanische Signal mit dem zu schwachen Informationsfluss (Sub-threshold Signal). Dieser wird durch den galvanischen Rauschreiz angeregt (Sub-threshold Signal + nGVS), wodurch der Schwellenwert des nicht-linearen Systems auch von eigentlich zu schwachen Signalen überschritten werden kann. Infolgedessen stehen dem Gehirn nun auch unterschwellige Reize zur Verarbeitung zur Verfügung (31, 32).

Im vorliegenden Fall ist die nGVS, die das Gleichgewichtsorgan stimuliert, von Interesse. Vorangegangene Studien zeigen, dass sich die nGVS positiv auf die statische Stabilität im Stehen von Gesunden und BVP-Patienten auswirkt (27). Außerdem kann die dynamische Balance während des Gehens nachweislich verbessert werden (33). Interessant ist auch, dass die räumliche Orientierung verbessert werden kann (34).

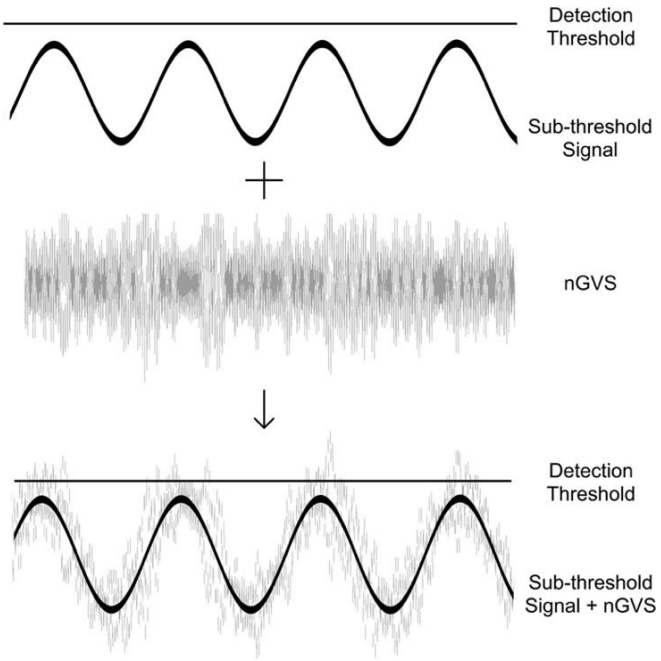

Abbildung 1: Stochastische Resonanz: Wenn nGVS am vestibulären System angelegt wird, kann die Verarbeitung von unterschwelligen Reizen durch stochastische Resonanz möglich werden (32)

2.3. Bewegungswahrnehmung

Um die Wirkweise der GVS und die Pathophysiologie der BVP besser zu verstehen ist es relevant, die Funktion des Gleichgewichtsorgans im Gesunden zu kennen. Es sorgt dafür, dass Beschleunigungen im menschlichen Körper wahrgenommen werden. Das Gleichgewichtsorgan befindet sich im Innenohr und umfasst die beiden senkrecht zueinander stehenden Otolithenorgane Macula sacculi und Macula utricculi, sowie die drei im rechten Winkel zueinanderstehenden Bogengänge (siehe Abbildung 2, oben). Die Bogengänge erkennen Drehbeschleunigungen, während die Makulaorgane geradlinige Translationsbeschleunigungen detektieren und zusätzlich die Ausrichtung des Kopfes zur Schwerkraft messen. Sie sind mit Endolymphe gefüllt und enthalten ein Epithel aus Sinneszellen, die sogenannten Haarzellen. Sie tragen apikal je ein Kinozilium und mehrere Stereovili (35).

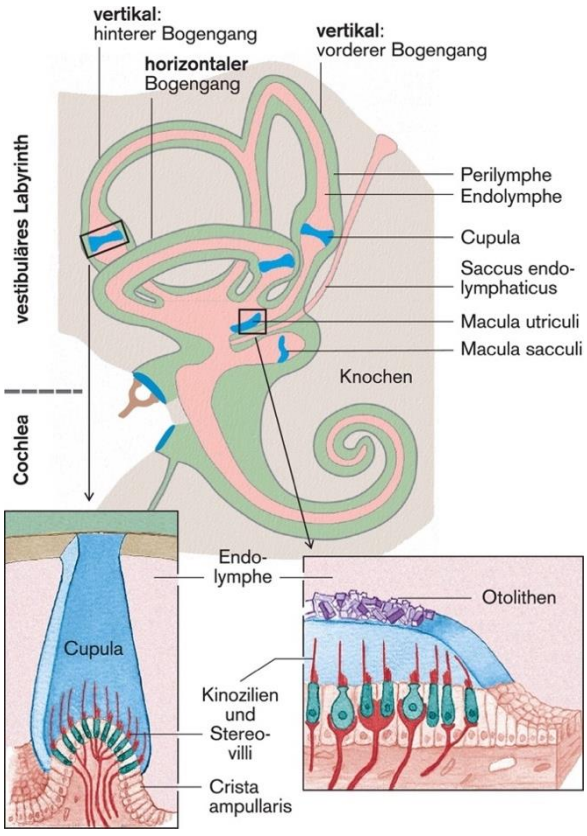

Abbildung 2: Schema des Labyrinths im Innenohr (rechtes Labyrinth von lateral vorne): Die Endolymphe (rot) und die Perilymphe (grün) des vestibulären Labyrinths und der Cochlea stehen miteinander in Verbindung (36).

In den Makulaorganen liegt dem Sinnesepithel eine Membran auf, auf der sich feine Kristalle aus Kalziumkarbonat befinden, die sogenannten Otolithen (siehe Abbildung 2, unten rechts). Je nach Lage des Kopfes oder bei geradlinigen Bewegungen folgt die Otolithenmembran der Schwerkraft oder der Bewegung. Dies verursacht eine Auslenkung der Kinozilien und dadurch eine Reizung der Haarzellen (36).

In den Bogengängen ist der Aufbau etwas anders als in den Makulaorganen. Das Sinnesepithel ist von einer gallertartigen Masse, der Cupula, bedeckt. Diese ist von der Endolymphe umgeben (siehe Abbildung 2, unten links). Bei Drehbewegungen bleibt die Endolymphe durch Trägheit in Ruhe, was zu einer Druckänderung und daraufhin Bewegung der Cupula führt. Die Bewegung überträgt sich auf die in die Cupula eingebetteten Kinozilien der Haarzellen (36).

Die Auslenkung der Kinozilien sowohl in den Makulaorganen als auch in den Bogengängen führt zu einem Einstrom endolymphatischen Kaliums in die Haarzellen, was eine Depolarisation der Zellen zur Folge hat. Am basalen Ende der Zellen führt dies über einen Calciumeinstrom zur Freisetzung des Neurotransmitters Glutamat. Dadurch erfolgt eine Erregung der afferenten Nervenfasern (36). Die Information gelangt dann über den Nervus vestibularis in die Vestibulariskerne im Hirnstamm. Von dort aus werden Signale in viele verschiedene Bereiche des Gehirns geleitet und schließlich verarbeitet. Die wichtigsten Ziele sind die kontralateralen Vestibulariskerne, die Augenmuskelkerne, das Kleinhirn, das Rückenmark, der Thalamus und die Verschaltung mit der Stützmotorik (35).

Bei der in dieser Arbeit thematisierten BVP handelt es sich um einen peripheren Ausfall des Gleichgewichtsorgans. Es liegt also eine Schädigung der Haarzellen und/oder der afferenten Nervenfasern des Nervus vestibularis vor (12).

Die GVS wirkt nach derzeitigem Wissensstand durch die Stimulation sowohl einiger afferenter Fasern des Nervus vestibularis, als auch der Membran der Haarzellen (21). Daraus ergibt sich, dass für den suffizienten Einsatz der GVS noch eine Restfunktion des Gleichgewichtsorgans vorhanden sein muss.

2.3.1. Bewegungsplattform

Zum objektiven Vergleich der Funktionsfähigkeit des Gleichgewichtsorgans bei verschiedenen Personen kann eine spezielle Bewegungsplattform genutzt werden. Mit dieser misst man, wie klein eine Bewegung oder Beschleunigung sein darf, sodass ein Mensch sie immer noch wahrnehmen kann. Durch gezielte Bewegungen in einer bestimmten Ebene wird der Schwellenwert für die Signaldetektion eines Bogengangs, des Utricculus oder des Sacculus separiert bestimmt. Dabei reduziert man den Bewegungsumfang, bis ein Punkt erreicht ist, an dem die Richtung der Bewegung nur noch erraten werden kann (37, 38). Bei BVP-Patienten liegt diese Wahrnehmungsschwelle höher als bei Gesunden (39). Auch diese Methode fand in der vorliegenden Studie Anwendung.

2.4. Ziele und Zusammenhänge

Die Studien dieses Promotionsvorhabens bauen auf den erfolgreichen vorangegangenen Studien zur Wirkung von nGVS bei BVP-Patienten auf. Die Erkenntnisse der Forschung sollten praktisch angewandt und in die aktuelle Therapie integriert werden. Folgende Forschungsfragen wurden in den Arbeiten formuliert und bearbeitet:

1) Führt die vestibuläre Rehabilitationstherapie (VRT) mit gleichzeitiger Anwendung von nGVS bei Patienten mit BVP zu einem besseren Resultat als eine Sham Stimulation während der VRT?

2) Zeigt sich bei der oben genannten Therapie eine Verbesserung der posturalen Kontrolle, eine Verminderung der subjektiv wahrgenommenen Beeinträchtigung durch den Schwindel und eine verbesserte dynamische Balance mit besseren Gangparametern und signifikantem Unterschied bei Behandlung mit nGVS verglichen mit einer Sham Stimulation?

3) Können BVP-Patienten und gesunde Probanden kleinere Bewegungen auf der Bewegungsplattform wahrnehmen, wenn das Gleichgewichtsorgan gleichzeitig eine nGVS erfährt?

In der Studie 1 dieser Dissertation: „Combining vestibular rehabilitation with noisy galvanic vestibular stimulation for treatment of bilateral vestibulopathy“ (8), wurden 23 BVP-Patienten über zwei Wochen vestibulär-physiotherapeutisch behandelt. 12 davon erhielten gleichzeitig eine nGVS, während 11 davon nur eine Sham Stimulation erhielten. Vor der Therapie wurde eine Baseline-Messung durchgeführt, die nach der Therapie und weitere zwei Wochen später wiederholt wurde, um die Effekte der Therapie quantifizierbar zu machen. Es war sowohl eine subjektive als auch eine objektive Verbesserung nach dem vestibulären Training erkennbar. Ein signifikanter Unterschied zwischen nGVS und Sham-Stimulation konnte nicht festgestellt werden.

In der Studie 2 dieser Dissertation: „Noisy galvanic vestibular stimulation improves vestibular perception in bilateral vestibulopathy“ (9), wurde untersucht, ob der Effekt der nGVS bei BVP-Patienten auf der Bewegungsplattform gemessen werden kann. Hier konnte bei 8 von 11 Patienten eine deutliche Verbesserung durch die Stimulation festgestellt werden. Bei Patienten mit schlechteren Ausgangswerten ohne Stimulation war die Verbesserung dabei größer.

Ziel dieser Dissertation ist es, die Therapieoption der Galvanischen Vestibulären Rauschstimulation weiter zu erforschen. Die Ergebnisse weisen in Zusammenschau mit anderen Studien darauf hin, dass die nGVS eine Verbesserung der Lebensqualität von BVP-Patienten bei der Anwendung im alltäglichen Leben erreichen kann. Die vorliegenden Studien helfen zusammen mit bereits bestehender Forschung und zukünftigen Arbeiten, eine suffiziente Therapie für die Betroffenen zu finden.

3. Zusammenfassung

Patienten mit einer bilateralen Vestibulopathie (BVP) leiden an einem kompletten oder inkompletten Ausfall des peripheren Gleichgewichtssystems. Typische Symptome sind chronisches Ungleichgewicht mit posturaler Instabilität während des Stehens und Gehens, vor allem in Dunkelheit oder auf Unebenheiten. Kopf- und Körperbewegungen führen zu einem Verwackeln der visuell wahrgenommenen Umwelt, wodurch die Blickstabilisierung und das Halten der Balance erschwert werden (13). Dies führt häufig zu einer geringeren Lebensqualität und einem erhöhten Sturzrisiko (15). Die einzige derzeit mögliche Therapie für eine Verbesserung der Schwindelsymptomatik bei BVP-Patienten ist eine vestibuläre Rehabilitationstherapie (1). Die Langzeiteffekte dieser Intervention sind jedoch nicht ausreichend validiert (18).

Die vorliegende Dissertation beschäftigt sich mit der galvanischen vestibulären Rauschstimulation (nGVS), einer alternativen Therapieform für BVP-Patienten. Diese folgt dem Wirkprinzip der stochastischen Resonanz, welches annimmt, dass ein sensorisches System schwache eingehende Signale leichter wahrnehmen und verarbeiten kann, wenn dem System eine nicht wahrnehmbare Rauschstimulation zugefügt wird (6). In vorangegangenen Studien konnte durch eine transkutane Stimulation des Gleichgewichtsorgans eine Verbesserung der posturalen Kontrolle in Form eines stabileren Stand- und Gangbildes sowohl bei Gesunden, also auch bei BVP-Patienten nachgewiesen werden (2-5).

Auf diesen Erkenntnissen basierend wurden für diese Dissertation in der ersten Studie die nGVS mit der bisher üblichen Therapie der vestibulären Rehabilitation bei BVP-Patienten kombiniert angewandt (8). Es konnte sowohl subjektiv als auch objektiv ein positiver Effekt des vestibulären Trainings nachgewiesen werden, jedoch ohne signifikanten Unterschied zwischen stimulierten und nicht-stimulierten Patienten. In der zweiten Studie wurde die Bewegungswahrnehmung bei sitzenden BVP-Patienten mit und ohne nGVS verglichen (9). Hier konnte bei 73% eine deutliche Verbesserung der Wahrnehmungsschwellen durch die nGVS nachgewiesen werden.

Die Kombination von vestibulärer Rehabilitation und nGVS verbessert den therapeutischen Effekt nicht. Beide Therapieoptionen für sich sind aber von Nutzen für BVP-Patienten und könnten in Zukunft komplementär für eine bessere Lebensqualität der Patienten angewandt werden.

4. Abstract

Patients with bilateral vestibulopathy (BVP) are suffering from a complete or incomplete loss of function of peripheral vestibular structures, presenting with chronic dizziness including postural imbalance when standing or walking, especially in darkness or on uneven ground. Head or body movements cause blurring of the visual scene, which causes difficulties in gaze stabilization and keeping one's balance (13). In most patients, this results in a lower quality of life and a higher risk of falls (15). The only therapeutic option currently available to sufficiently improve the outcome for BVP patients is vestibular rehabilitation therapy (1). However, the long-term effects of this intervention are limited (18).

This thesis occupies with an alternative therapy for BVP patients, i.e. noisy galvanic vestibular stimulation (nGVS). It follows the mechanism of stochastic resonance, which is hypothesized to enhance the ability of a sensory system to detect and process weak signals if a subthreshold amplitude of noise is added (6). This way, nGVS transcutaneously delivered to the vestibular system of BVP patients has been shown to facilitate postural stabilization while standing or walking in healthy subjects as well as in patients with BVP (2-5).

Based on these findings, the first study of this thesis combined nGVS with the customary vestibular rehabilitation therapy on BVP patients (8). We could prove a positive effect of the vestibular rehabilitation training objectively measured as well as subjectively experienced by patients. However, there was no significant difference between stimulated and non-stimulated patients. In the second study we compared the ability of movement detection of BVP patients while seated with and without nGVS (9). Here we could detect an improvement of perception thresholds through nGVS in 73% of the participants.

The combination of vestibular rehabilitation therapy and nGVS does not improve the therapeutic effect. However, both therapy options on their own bring their benefit and might be suitable partners for a complementary treatment strategy to improve BVP patients´ quality of life.

5. Paper I

Combining vestibular rehabilitation with noisy galvanic vestibular stimulation for treatment of bilateral vestibulopathy

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Journal of Neurology (2022) 269:5731-5737

doi: 10.1007/s00415-022-11033-x

Journal of Neurology
https://doi.org/10.1007/s00415-022-11033-x

ORIGINAL COMMUNICATION

Combining vestibular rehabilitation with noisy galvanic vestibular stimulation for treatment of bilateral vestibulopathy

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Received: 29 October 2021 / Revised: 10 February 2022 / Accepted: 15 February 2022

Abstract

Objective Noisy galvanic vestibular stimulation (nGVS) has been shown to partly restore vestibular function and to stabilize stance and gait in patients with incomplete bilateral vestibulopathy (BVP). Here, we examined potential synergistic effects of nGVS when combined with standardized vestibular rehabilitation training (VRT).

Methods 23 patients with confirmed BVP received a 30-min vestibular rehabilitation training (VRT) program three times a week for 2 weeks. The intervention group ($n = 12$) was stimulated with nGVS (at individually determined optimal amplitudes) during training, whereas the control group ($n = 11$) received zero-amplitude nGVS (sham stimulation) during training. Outcome measurements assessed at baseline, after 2 weeks of training, and at 2-week follow-up included quantitative posturography, instrumented gait analysis, Timed Up and Go Test (TUG), Functional Gait Assessment (FGA), and clinical scores related to quality of life and balance confidence.

Results After 2 weeks of VRT, all patients showed moderate improvement in balance. Irrespective of nGVS treatment, performance improved in the TUG ($p < 0.013$), and in the FGA ($p < 0.040$). Furthermore, base of support when walking with closed eyes was reduced after 2-week training ($p < 0.003$). Postural sway did not change. There was no difference between groups and thereby no evidence for an additional influence of nGVS on the VRT treatment effects.

Conclusion nGVS does not induce synergistic treatment effects in combination with VRT in patients with BVP when applied during treatment sessions. Hence, rather than being applied in parallel, nGVS and VRT might be complementary therapeutic options with nGVS being used during postural activities in daily life, e.g., walking.

Keywords Bilateral vestibulopathy · Vestibular rehabilitation · Noisy galvanic vestibular stimulation · Balance · Gait

Introduction

Patients with bilateral vestibulopathy (BVP) suffer from a complete or incomplete loss of function of peripheral vestibular structures, presenting with chronic dizziness including postural imbalance when standing or walking, especially in darkness or on uneven ground. Head or body movements cause visual blurring or oscillopsia, i.e., illusionary bouncing of the visual scene, which causes difficulties in gaze stabilization and keeping one's balance [23]. In most patients, this results in a lower quality of life and a higher risk of falls [24]. The only therapeutic option currently available to sufficiently improve outcome for BVP patients is vestibular rehabilitation therapy (VRT), which aims to improve balance by the training of multisensory postural control to compensate and substitute the vestibular hypofunction [9]. However, the long-term effects of this intervention are limited [21].

Recently, white noise galvanic vestibular stimulation (nGVS) at imperceptible levels was used to modify vestibular perception and performance [5, 28]. When an optimal amplitude of noise is added to a nonlinear system, such as the vestibular system, a mechanism known as stochastic

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Published online: 25 February 2022

resonance is hypothesized to enhance the ability to detect and process weak signals [19] and hence to improve vestibular functions [16]. nGVS transcutaneously delivered to the mastoid processes has been shown to facilitate postural stabilization while standing or walking in healthy subjects as well as in patients with BVP [8, 29, 30]. This makes it a promising non-invasive treatment option for patients with peripheral vestibular hypofunction.

It is not known whether nGVS might induce beneficial synergistic effects when combined with VRT in patients with BVP. Hence, the primary goal of this study was to determine whether the application of nGVS during VRT promotes a better overall recovery than rehabilitation alone (i.e., during sham nGVS) in patients with BVP.

Methods

This double-blinded clinical explorative study aimed to evaluate the impact of imperceptible amounts of nGVS on the efficacy of vestibular rehabilitation in patients with BVP. The study protocol was approved by the ethics committee of the University of Munich and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent.

Subjects

Twenty-three patients (9 females, mean age 62.3 ± 14.3 years) participated in this study. All of them showed a clinically proven BVP, confirmed either by bilaterally reduced responsiveness to bithermal (44 and 30 °C) caloric irrigation (mean peak slow-phase velocity < 6 deg/s) or a pathological video head impulse test on both sides (gain < 0.6) [23].

Noisy galvanic vestibular stimulation

nGVS was delivered via a pair of conductive-rubber electrodes (4.0 cm × 6.0 cm), placed in two saline-soaked sponges, that were attached over the left and right mastoid process behind the participant's ears. Electrodes were connected to a portable direct current stimulator (neuroConn®, Ilmenau, Germany), which delivered the electrical signal consisting of a zero-mean Gaussian white noise within a frequency range of 0–30 Hz. To identify the individual optimal nGVS amplitude, each patient performed eight quiet-standing trials with eyes closed for a duration of 30 s on a stabilometer platform (Kistler 9261A, Winterthur, Switzerland). During each trial, patients received nGVS at a different intensity (from 0 to 700 µA in steps of 100 µA) in a randomized order and their performance during stimulation trials was compared to their baseline performance (i.e., nGVS at 0 µA). Improvement in balance performance due to nGVS was determined based on the three different posturography parameters, i.e., mean velocity, area, and root mean square of sway. The stimulation amplitude at which individual patients exhibited the best improvement in all three parameters was assigned as their 'optimal nGVS amplitude'. For the sham condition of nGVS, the intensity of the electrical signal was set to 0 µA.

Vestibular rehabilitation therapy

The rehabilitation program was individually adjusted to the deficits and therapeutic demands of each patient, to ensure that VRT exercises were sufficiently challenging to induce treatment effects [26]. The basic exercises included training of gaze stabilization during standing and walking and eye–head coordination during standing and walking as well as practices to optimize balance strategies. To challenge patients even more, exercises could be performed on foam or with eyes closed. Furthermore, several different tasks were combined with each other or performed while walking. These basic exercises were individually adapted to the main demands of each patient. This way, the VRT program specifically targeted the individual physical problems. Each therapy session was guided and supervised by an expert vestibular physical therapist and lasted 30 min.

Procedures

Participants were randomly assigned to one of two groups. The intervention group received nGVS during VRT; the control group received sham stimulation during VRT. In both trial arms, patients were provided with a VRT program three times a week for 2 consecutive weeks (30 min rehabilitation per session). For patients in the intervention group, nGVS was active during all rehabilitation sessions. Patients in the control group received sham nGVS during each rehabilitation session. Outcome measures were assessed at baseline (T0), after 2 weeks of training (T1) and at 2-week follow-up (T2) (see Fig. 1).

Outcome measures

Several balance and gait tests and questionnaires were applied at the three assessment time points (T0–T2). Primary outcome was postural stability as assessed during posturography while standing on foam with eyes closed. The amount of body sway was quantified by the mean velocity of sway. Secondary outcomes were the patient's gait performance, mobility, and dynamic balance. Gait assessment was performed on a pressure-sensitive gait mat (GAITRite®, CIR System, Sparta, NJ, USA) while walking with eyes closed. Gait performance was evaluated

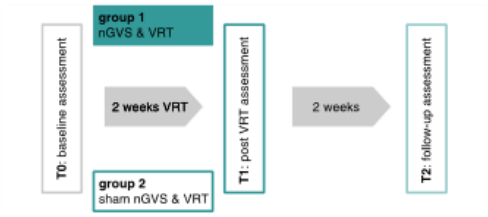

Fig. 1 Scheme of the study protocol. Following an initial baseline assessment, patients were randomly assigned to an intervention group (group 1) or a control group (group 2). Group 1 received 2 weeks of VRT with nGVS at optimal intensity, while group 2 received sham stimulation during training. Treatment effects were assessed immediately after 2 weeks of training (T1) and at 2-week follow-up. *nGVS* noisy galvanic vestibular stimulation, *VRT* vestibular rehabilitation therapy

by quantifying walking velocity, base of support, and the coefficient of variation (CV) of stride time. Patients' functional mobility and dynamic balance were assessed by the Berg Balance Scale (BBS; max. 56) [13], the Functional Gait Assessment (FGA; max. 30) [27], and the Timed Up and Go Test (TUG; times of > 13.5 s are related to an increased risk of falling in older adults) [3]. Additionally, patients completed the following questionnaires: the Dizziness Handicap Inventory (DHI; 16–34 points = mild handicap, 36–52 points = moderate handicap), > 54 points = severe handicap) [13] to evaluate the self-perceived handicap due to dizziness, the International Physical Activity Questionnaire (IPAQ; low, moderate, or high physical activity score) [18] to score the level of physical activity, the Falls Efficacy Scale International (FES-I; max. 64) [10] to assess balance confidence and fear of falling, and the Activities-specific Balance Scale (ABC-d; max. 100%) [13] to assess confidence in performing daily activities.

Statistical analysis

Data are reported as mean ± SD. Since most of the outcome measures did not exhibit normal distribution, nonparametric tests were performed to assess differences in treatment effects between the intervention and control groups. For all outcome parameters, the Friedman test was used to assess treatment effects between the three assessment time points (T0, T1, T2). Significant treatment effects were subsequently compared between the intervention and control groups using the Mann–Whitney *U* test. Results were considered significant if $p < 0.05$. Statistical analysis was performed using SPSS (Version 26.0, IBM Corp., USA).

Table 1 Characterization of the study cohorts

	Intervention group	Control group	
Age	61.92 ± 15.93 y	62.64 ± 13.15 y	$p = 0.926$
Gender	4 f/8 m	5 f/6 m	$p = 0.552$
SPV (during caloric irrigation)	5.055 ± 6.854°/s	5.650 ± 3.188°/s	$p = 0.080$
vHIT gain	0.280 ± 0.215	0.379 ± 0.213	$p = 0.184$
Disease duration	6.41 ± 8.85 y	10.33 ± 12.81 y	

f female, *m* male, *SPV* slow-phase velocity, *y* years

Results

Characterization of the study cohort

The study cohort consisted of 23 patients with a clinically proven BVP. The random assignment of these patients to either the intervention group or the control group yielded two homogenous cohorts with respect to age and gender distribution, vestibular hypofunction, and balance deficits (see Tables 1, 2). The results of the questionnaires filled by the patients resulted in subjective as well as objective moderate dizziness which did not change significantly during the period of the study (see Table 2).

General effects of VRT

To examine general effects of VRT, we analyzed training effects on each outcome measure at T1 (after 2 weeks of training) and T2 (at 2-week follow-up) compared to baseline T0. Figure 2 shows in the left panel measurements at baseline (T0), post VRT (T1), and at follow-up (T2) for all participants (sham and intervention group). We did not find VRT-induced changes on postural stability measured by posturography, the BBS scale or any of the balance confidence or physical-activity-related questionnaires. In contrast, we found a moderate training effect regarding patients' gait performance: When walking with closed eyes, the base of support was significantly smaller ($p < 0.003$) at T1 and returned to baseline level at T2 (see Fig. 2, B, left panel). Comparable improvements were further found for tests of functional mobility, i.e., the TUG ($p < 0.013$) and the FGA ($p < 0.040$) that remained stable at follow-up assessment (see Fig. 2C, D, left panel).

Effects of nGVS

Identification of optimal nGVS intensity yielded an average nGVS amplitude of 330 ± 203 µA. None of the participants felt pain or any other negative symptoms during the application of nGVS. The intervention group received nGVS at

Table 2 Results of assessments

	Intervention group	Control group	
T0—sway velocity (standing on foam, eyes closed)	313.840 ± 204.215 cm/s	556.167 ± 287.200 cm/s	$p = 0.056$
T1—sway velocity (standing on foam, eyes closed)	263.421 ± 166.910 cm/s	501.692 ± 275.694 cm/s	$p = 0.023$
T2—sway velocity (standing on foam, eyes closed)	332.191 ± 171.511 cm/s	550.593 ± 249.715 cm/s	$p = 0.036$
T0—gait velocity (walking with eyes closed)	61.833 ± 26.012 cm/s	63.503 ± 25.271 cm/s	$p = 0.712$
T1—gait velocity (walking with eyes closed)	65.949 ± 26.640 cm/s	66.919 ± 22.080 cm/s	$p = 0.758$
T2—gait velocity (walking with eyes closed)	61.147 ± 26.755 cm/s	65.438 ± 24.439 cm/s	$p = 0.951$
T0—stride time CV (walking with eyes closed)	18.240 ± 13.991%	11.580 ± 7.695%	$p = 0.097$
T1—stride time CV (walking with eyes closed)	16.129 ± 19.920%	10.532 ± 7.052%	$p = 0.498$
T2—stride time CV (walking with eyes closed)	11.350 ± 5.474%	15.126 ± 13.450%	$p = 1.000$
T0—base of support (walking with eyes closed)	20.962 ± 6.117 cm	20.417 ± 7.442%	$p = 0.667$
T1—base of support (walking with eyes closed)	19.000 ± 5.791 cm	19.625 ± 6.258 cm	$p = 1.000$
T2—base of support (walking with eyes closed)	21.556 ± 5.306 cm	20.277 ± 6.277 cm	$p = 0.389$
T0—TUG	7.985 ± 2.676 s	6.947 ± 1.260 s	$p = 0.468$
T1—TUG	7.450 ± 2.892 s	6.292 ± 1.287 s	$p = 0.391$
T2—TUG	7.190 ± 2.515 s	6.412 ± 0.987 s	$p = 0.356$
T0—FGA	23.417 ± 4.963	23.000 ± 3.194	$p = 0.805$
T1—FGA	23.667 ± 4.030	26.091 ± 2.737	$p = 0.137$
T2—FGA	24.917 ± 4.166	25.636 ± 2.942	$p = 0.877$
T0—DHI	40.833 ± 17.837	42.727 ± 14.867	$p = 0.734$
T1—DHI	39.333 ± 21.309	44.000 ± 17.550	$p = 0.423$
T2—DHI	36.667 ± 18.884	43.818 ± 20.851	$p = 0.423$
T0—BBS	49.167 ± 6.645	50.273 ± 4.268	$p = 0.951$
T1—BBS	50.250 ± 6.369	50.818 ± 4.750	$p = 0.975$
T2—BBS	49.750 ± 6.152	51.364 ± 3.982	$p = 0.733$
T0—ABC-d	69.245 ± 26.027	78.693 ± 17.255	$p = 0.372$
T1—ABC-d	75.219 ± 21.443	70.881 ± 22.502	$p = 0.601$
T2—ABC-d	74.542 ± 20.264	76.421 ± 13.406	$p = 0.902$
T0—FES-I	25.000 ± 6.396	25.727 ± 9.717	$p = 0.805$
T1—FES-I	24.083 ± 6.921	26.364 ± 9.233	$p = 0.557$
T2—FES-I	24.333 ± 5.662	26.636 ± 10.957	$p = 0.902$

CV coefficient of variation, *TUG* timed up and go test; *FGA* Functional Gait Assessment, *DHI* Dizziness handicap inventory, *BBS* Berg Balance Scale, *ABC-d* Activities-specific Balance Scale, *FES-I* Falls Efficacy Scale International

optimal intensities during the complete duration of VRT, while the control group received sham nGVS (i.e., 0 μA) during training. Combining nGVS with VRT did not have any effect on the examined outcome measures after 2 weeks of training or after the 2-week follow-up assessment (see Fig. 2, right panel).

Discussion

Stochastic electrical vestibular stimulation at imperceptible intensities (i.e., nGVS) has been demonstrated to stabilize static posture and walking performance in patients with BVP [6, 11, 22]. Up to now, vestibular rehabilitation (i.e., VRT) is the only established treatment option for patients with BVP [1]. Here, we applied nGVS in addition to a standardized VRT treatment in a placebo-controlled double-blinded clinical study to examine whether the combination of both treatments would yield any synergistic effects. While VRT generally induced moderate improvements in patients' balance capabilities, we found no evidence that the combination of nGVS with VRT yields any additional effects on either patients' balance capabilities or their subjective balance self-confidence. These results will be discussed with respect to (1) the general effects of vestibular rehabilitation training, (2) the absence of any synergistic effects from nGVS, and (3) considerations on whether and how to use both treatment strategies together in the future.

Two weeks of VRT yielded only moderate balance improvements in patients with respect to clinical tests of functional mobility, i.e., the TUG and FGA, and improved gait performance while walking with closed eyes. However,

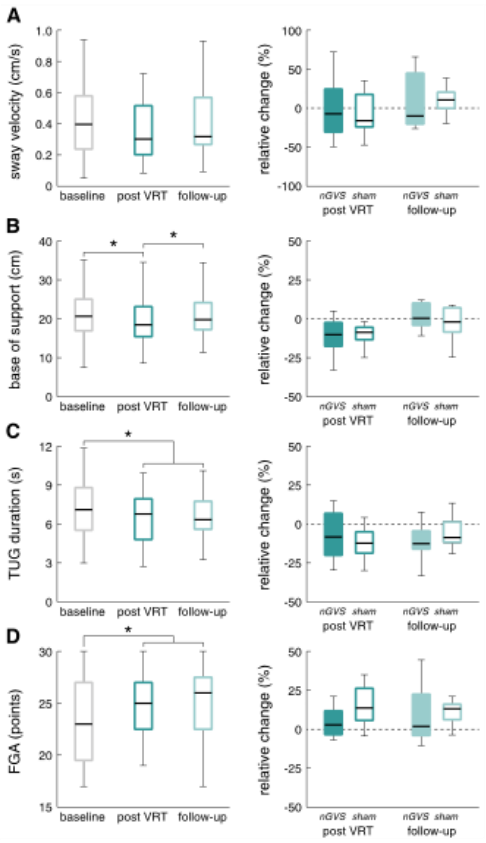

Fig. 2 VRT and nGVS treatment effects. Left panel: general VRT-related treatment effects (for the combined intervention and control group) at T1 (post VRT) and T2 (follow-up) compared to T0 (baseline assessment) for **A** sway velocity while standing on foam with eyes closed, **B** base of support while walking with eyes closed, **C** TUG, and **D** the FGA. Right panel: comparison of relative changes in the respective outcome measures between the intervention and control groups. Moderate general treatment effects of VRT were found for gait capacity, TUG and FGA performance, but not for static posturography. Treatment effects did not differ between the intervention and control groups. *VRT* vestibular rehabilitation therapy; *nGVS* noisy galvanic vestibular stimulation, *TUG* timed up and go test, *FGA* functional gait assessment; *Indicates a significant difference

no effects were found with respect to clinical scores on balance confidence or static posturography—the primary outcome measure of this study. This observation is in contrast to earlier reports which found clear VRT treatment effects on static body sway and related outcome measures [13]. This discrepancy could be due to differences in the specific VRT protocol and/or differences in study cohorts. For instance, VRT in the present study only lasted for 2 weeks, while in previous studies, VRT was often applied for considerably longer periods, which might account for treatment effects in BVP [2, 13, 17]. Another reason for the observed weakness of VRT treatment effects could be that patients in our cohort had a relatively moderate severity of BVP-related symptoms compared to previous studies [3] and might therefore only exhibit weak responses when treated with VRT.

Combining nGVS with VRT did not yield any additional effects on patients' stance or gait performance or their balance self-confidence. This absence of synergistic effects of nGVS with VRT might be related to the mode of action of imperceptible stochastic vestibular stimulation, which is thought to improve vestibular function by stochastic resonance, a mechanism in which subthreshold sensory signals become enhanced and detectable by the addition of a particular non-zero amount of noise [4]. Accordingly, nGVS has been shown to particularly improve the perception of weak, subthreshold vestibular cues [15, 16] and vestibular-related balance function during absent (i.e., quiet standing [12]) or slow head movements (i.e., slow walking [29, 30]). In contrast, nGVS affected neither vestibular-related perception of suprathreshold cues nor balance function in the presence of dynamic and fast head kinematics in the previous studies. On the other hand, VRT particularly focuses on strong vestibular cues and rapid head movements in order to train deficient vestibular-related balance and ocular-motor functions [25]. Hence, both approaches operate on the opposing ends of the vestibular signal spectrum, which makes them unlikely to exhibit any positive or negative interference effects.

Another reason for the absence of nGVS effects on balance performance and/or confidence could be the point in time at which treatment effects were assessed in this study. Accordingly, assessment of treatment effects at T1 and T2 took place 1 day and 2 weeks after cessation of nGVS, respectively. There is so far no consensus about whether nGVS only acts during ongoing stimulation or whether it exhibits any plastic aftereffects after cessation of stimulation. In favor of the later assumption, Fujimoto et al. reported in an uncontrolled study long-term effects of nGVS on postural stability that lasted up to 6 h after cessation of stimulation [7]. Later, placebo-controlled studies did not find any evidence for long-term effects of nGVS on vestibular function [14, 20]. Irrespective of this question, our first assessment of treatment effects took place more than 12 h after the last application of nGVS and might have thus missed any potential nGVS-induced effects during ongoing stimulation or shortly after stimulation.

The observed absence of any synergistic treatment effects in the combination of VRT with nGVS does, however, not preclude a joint application of both therapeutic strategies for future treatment of BVP. As outlined above, both treatment approaches follow distinct therapeutic principles, target

rather different sources of deficit in BVP, and act on differing timescales. VRT is usually applied intermittently with the aim to recruit visual and proprioceptive cues to establish a long-term sensory substitution of adaptation for vestibular impairment in BVP, while nGVS only acts during ongoing stimulation with the aim to directly improve the impaired processing of weak vestibular cues in BVP. Hence, both therapeutic options might be suitable partners for a complementary treatment strategy in BVP.

Acknowledgements The authors thank Katie Göttlinger for copy-editing the manuscript.

Author contributions KJ, MW, and AK designed the study protocol. AK, TA, and KJ wrote the ethics application and obtained the ethics vote from LMU. JE, SK, TA, and JD recruited patients. JD and KJ supervised the clinical evaluation of the patients. JE, SK, TA, and AK performed the study on patients. VRT was delivered by SK. JE, AK, and MW analyzed the data. JE wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL. NeuroConn (Ilmenau, Germany) provided the mobile DC-stimulator with the protocol for noisy galvanic vestibular stimulation. The study was supported by the German Federal Ministry for Education and Research (BMBF IFB 01EO1401).

Declarations

Conflicts of interest KJ received speakers' honoraria from Schwabe Pharma and Rölke Pharma. KJ and MW received funding from NeuroConn (DC-stimulator). On behalf of all authors, the corresponding author states that there is no other conflict of interest.

Ethical approval This double-blinded clinical explorative study aimed to evaluate the impact of imperceptible amounts of nGVS on the efficacy of vestibular rehabilitation in patients with BVP. The study protocol was approved by the ethics committee of the University of Munich and was conducted in accordance with the Declaration of Helsinki.

Informed consent All participants gave their written informed consent.

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6. Paper II

Noisy galvanic vestibular stimulation improves vestibular perception in bilateral vestibulopathy

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Journal of Neurology (2023) 270:938-943

doi: 10.1007/s00415-022-11438-8

Journal of Neurology (2023) 270:938–943
https://doi.org/10.1007/s00415-022-11438-8

ORIGINAL COMMUNICATION

Noisy galvanic vestibular stimulation improves vestibular perception in bilateral vestibulopathy

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Received: 25 September 2022 / Revised: 17 October 2022 / Accepted: 18 October 2022 / Published online: 2 November 2022

Abstract

Background Patients with bilateral vestibulopathy (BVP) suffer from impaired vestibular motion perception that is linked to deficits in spatial memory and navigation.

Objective To examine the potential therapeutic effect of imperceptible noisy galvanic vestibular stimulation (nGVS) on impaired vestibular perceptual performance in BVP.

Methods In 11 patients with BVP (mean age: 54.0 ± 8.3 years, 7 females), we initially determined the nGVS intensity that optimally stabilizes balance during a static posturographic assessment. Subsequently, effects of optimal nGVS vs. sham stimulation on vestibular motion perception were examined in randomized order. Vestibular perceptual performance was determined as direction recognition thresholds for head-centered roll tilt motion on a 6DOF motion platform in the absence of any visual or auditory motion cues.

Results For each patient, an nGVS intensity that optimally stabilized static balance compared to sham stimulation could be identified (mean 0.36 ± 0.16 mA). nGVS at optimal intensity resulted in lowered vestibular perceptual thresholds (0.94 ± 0.30 deg/s) compared to sham stimulation (1.67 ± 1.11 deg/s; $p = 0.040$). nGVS-induced improvements in vestibular perception were observed in 8 of 11 patients (73%) and were greater in patients with poorer perceptual performance during sham stimulation ($R = -0.791$; $p = 0.007$).

Conclusions nGVS is effective in improving impaired vestibular motion perception in patients with BVP, in particular in those patients with poor baseline perceptual performance. Imperceptible vestibular noise stimulation might thus offer a non-invasive approach to target BVP-related impairments in spatial memory, orientation, and navigation.

Keywords Bilateral vestibulopathy · Galvanic vestibular stimulation · Stochastic resonance · Vestibular perception · Balance

Introduction

Bilateral vestibulopathy (BVP) is characterized by a chronic reduced or absent bilateral vestibular function [1]. Patients primarily suffer from postural imbalance during standing and walking that worsens in darkness or on uneven ground and blurred vision induced by head movements (i.e., oscillopsia) [2–4]. Beyond, their impaired perceptual registration of head orientation and motion in space has been linked to deficits in spatial memory and navigation [5–7]. BVP-related symptoms considerably impact patients' daily activities and mobility [8], are associated to reduced quality of life [9] and an increased risk of recurrent falling [8, 10]. The general long-term prognosis of BVP is poor [11], and available treatment options are currently limited to physical therapy that can yield, if any, only partial compensation for lost vestibular function [12].

A majority of patients with BVP typically retain residual vestibular excitability and function [13, 14]. Within recent years, attempts have been made to augment and boost residual vestibular excitability in BVP by means of an imperceptible vestibular noise stimulation using non-invasive noisy galvanic vestibular stimulation (nGVS) [15, 16]. The rationale behind these attempts is stochastic resonance (SR)—a phenomenon according to which (pathologically

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increased) thresholds for sensory information processing can be lowered by application of an appropriate amount of low-intensity sensory noise [17, 18]. Previous studies could demonstrate that treatment with nGVS effectively improves vestibulospinal function [19, 20] and as a result stabilizes impaired balance [21, 22] and gait performance [23, 24] of patients with BVP. While nGVS-related treatment attempts in BVP so far focused on impaired postural regulation, recent evidence from healthy individuals indicates that nGVS might also directly affect vestibular perceptual performance [25–28] and could thus be effective to treat BVP-related deficits in spatial cognition.

In the current study, we examined the effects of imperceptible nGVS vs. sham stimulation on vestibular perceptual performance in patients with BVP. We demonstrate that nGVS effectively improves vestibular motion perception in particular in those patients with poor baseline perceptual performance. nGVS might thus provide a non-invasive and well-tolerated treatment option to target a wide range of BVP-related symptoms including non-motor deficits in spatial memory and navigation.

Methods and materials

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the ethics committee of the University of Munich (study ID: 20-1137) and registered at DRKS (DRKS00024660). Each patient gave written informed consent prior to participation.

Participants

Eleven patients with BVP (mean age: 54.0 ± 8.3 years, 7 females) participated in the study. All patients showed a clinically proven deficit, i.e., a bilateral pathological video head impulse test (vHIT, horizontal gain < 0.6) and/or bilateral reduced or absent caloric responses (sum of maximal peak velocities of the slow-phase nystagmus with cold and warm water < 6 deg/s) [1]. Detailed clinical characteristics of patients are presented in Table 1.

Galvanic vestibular stimulation

Vestibular noise stimulation (i.e., nGVS) was applied via a pair of 4.0 cm × 6.0 cm Ag–AgCl electrodes attached bilaterally over the left and right mastoid process. Zero-mean Gaussian white noise stimulation with a frequency range of 0–30 Hz and varying peak amplitudes of 0–0.7 mA was delivered by a mobile constant current stimulator (neuroConn®, Illmenau, Germany).

Experimental procedures

The experimental procedures consisted of two parts: Initially, for each patient the nGVS intensity that optimally stabilized body balance as assessed by static posturography was individually identified. In the main part, the effect of nGVS at this optimal intensity on vestibular motion perception was assessed in comparison with sham stimulation (i.e., nGVS at 0 mA).

The initial identification of optimal nGVS intensity was performed in analogy to previous procedures [22, 28]: Body

Table 1 Clinical characteristics, stimulation characteristics and effects

Patient	Sex	Age	Etiology	Caloric response, deg/s[a]		vHIT gain		nGVS, mA	Perceptual threshold, deg/s	
				Left	Right	Left	Right		Sham	nGVS
P1	m	46	Genetic	4.1	5.2	0.04	0.12	0.2	0.71	1.05
P2	f	57	Idiopathic	2.6	2.4	0.74	0.67	0.7	4.34	1.31
P3	f	52	Idiopathic	4.4	2.6	0.18	0.16	0.6	1.89	0.81
P4	m	54	Idiopathic	2.7	0.7	0.32	0.22	0.2	1.25	1.35
P5	m	54	Idiopathic	3.0	4.9	0.18	0.02	0.2	0.73	0.71
P6	f	55	Genetic	5.7	2.5	0.22	0.15	0.4	2.72	1.15
P7	f	63	Idiopathic	2.5	4.4	0.11	0.03	0.4	1.62	1.20
P8	f	60	Ototoxic	13.8	7.4	0.31	0.32	0.3	2.08	0.69
P9	f	65	Idiopathic	3.3	2.6	0.66	0.34	0.4	0.39	0.56
P10	m	37	Idiopathic	7.5	12.0	0.53	0.15	0.2	1.11	1.03
P11	f	45	Ototoxic	3.5	3.3	0.30	0.26	0.3	1.49	0.52

vHIT video head impulse test, *nGVS* noisy galvanic vestibular stimulation

[a]Sum of maximal slow phase eye velocity during warm and cold caloric irrigation

sway was recorded for 30 s on a posturographic force plate (Kistler, 9261A, Kistler Group, Winterthur, Switzerland) at 40 Hz while patients were standing with their eyes closed. This procedure was repeated eight times, while patients were stimulated with a different amplitude of nGVS (ranging from 0–0.7 mA, in a pseudo-randomized order) in each trial. Patients were blinded to the stimulation order and were given short breaks between trials to recover. Body sway during each trial was characterized by three different body sway measures: the mean velocity of the center of pressure (CoP) motion, the root mean square of CoP movement, and the envelopment area traced by the CoP [22]. The optimal nGVS intensity was determined as the one that yielded greatest reduction in all three body sway measures compared to sham stimulation (i.e., nGVS at 0 mA).

In the main part, effects of nGVS at optimal intensity on vestibular perceptual thresholds were examined. Vestibular perceptual thresholds were determined as direction recognition thresholds (DRT) for head-centered roll tilt motion in analogy to previous procedures [25–28]. Perception of this motion requires the integration of cues from the semicircular canals and the otoliths of the peripheral vestibular endorgans [29]. Patients were secured in a chair mounted on 6DOF motion platform (Moog 6DOF2000E, East Aurora, New York) by a five-point harness and an adjustable head restraint. The experiment was performed in total darkness and patients wore noise-cancelling headphones to minimize the presence of non-vestibular sensory cues [30]. The complete procedure comprised 150 trials. Each trial consisted of a head-centered roll tilt motion made of a single half-cycle acceleration that followed a raised-cosine velocity profile (Fig. 1A) at 1 Hz to either the left or right (in randomized order), and patients had to indicate the direction of perceived motion by button press. The peak motion velocity of each trial was varied following an adaptive 3-down 1-up staircase procedure. Subsequently, a cumulative Gaussian psychometric curve was fitted to the response data of all trials and the resultant DRT was determined as the magnitude of roll tilt velocity, which could be distinguished at a rate of 79.4% [31]. DRTs were determined in two sessions, once during nGVS delivered at optimal intensity and once during sham stimulation (i.e., nGVS at 0 mA) in a pseudo-randomized order. Patients were blinded to the stimulation order and were given an extended break to recover in-between sessions.

Data and statistical analysis

Data are reported as mean ± SD. Effects of nGVS on vestibular perceptual thresholds were examined using a one-way repeated measures analysis of variance (ANOVA) with the factor stimulation (nGVS vs. sham). Pearson's correlations were performed to test for any association between clinical test outcomes (caloric response, vHIT gain), baseline thresholds, and nGVS-induced changes in thresholds. Results were

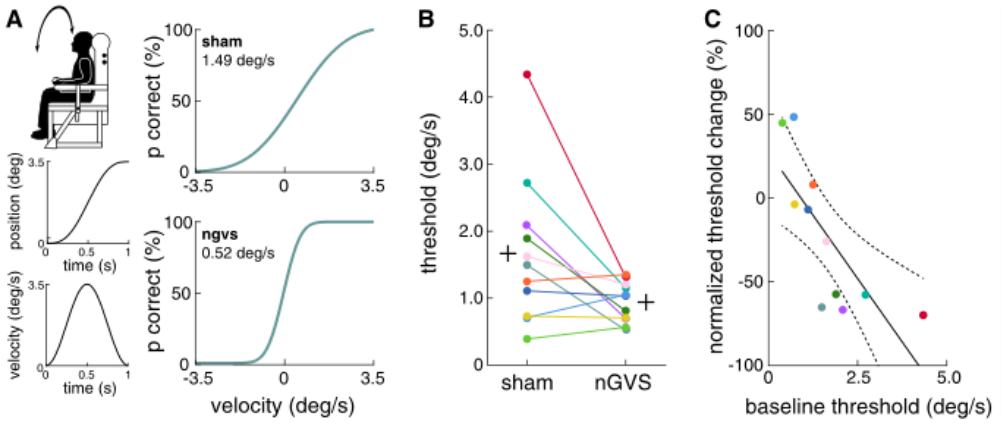

Fig. 1 Effects of nGVS on vestibular perceptual thresholds for head-centered roll tilt motion. (**A**) Left panel: Vestibular perceptual thresholds were determined on a 6DOF motion platform with patients secured in a platform-mounted chair. Arrow indicates the rotational axis alongside the typical displacement and velocity profile of motion stimuli applied during psychophysical testing. Right panel: Exemplary psychometric curves of perceptual performance and corresponding thresholds during sham (i.e., nGVS at 0 mA) and optimal nGVS (patient P11). (**B**) Group effects of nGVS on perceptual thresholds revealed an improved perceptual performance compared to sham stimulation ($p = 0.04$; black crosses represent the group average for each condition). (**C**) Higher baseline perceptual thresholds during sham stimulation were associated to greater nGVS-induced improvements in perceptual performance ($R = -0.791$; $p = 0.007$)

considered significant at $p < 0.05$. Statistical analysis was performed using SPSS (Version 26.0, IBM Corp., USA).

Data availability

Data reported in the article will be shared by any appropriately qualified investigator on request after pseudonymization.

Results

Administration of nGVS at intensities ranging from 0–0.7 mA was well tolerated and did not cause disequilibrium in any of the examined patients. For each patient, we identified an optimal nGVS intensity at which static balance was effectively stabilized (optimal nGVS intensity mean 0.36 ± 0.16 mA, range 0.2–0.7, Table 1). Compared to sham stimulation, stimulation at optimal nGVS reduced body sway velocity by $25 \pm 14\%$, the root mean square of body sway by $22 \pm 18\%$, and body sway area by $32 \pm 26\%$. Stimulation at optimal nGVS intensity was not perceived by any patient.

Psychophysical assessment of baseline perceptual thresholds for head-centered roll tilt motion during sham stimulation (i.e., nGVS at 0 mA) yielded an average threshold level of 1.67 ± 1.11 deg/s, which closely corresponds to the range of previously reported thresholds in patients with BVP [32]. Baseline perceptual thresholds of patients were not associated to any of the clinical outcomes from vestibular function tests (i.e., caloric response or vHIT gain).

Application of nGVS at optimal intensity resulted in lowered perceptual thresholds ($F_{1,10} = 5.58$; $p = 0.040$; effect size: $\eta^2_p = 0.36$) in 8 of 11 patients (73%, Fig. 1B). Vestibular thresholds during nGVS were found at 0.94 ± 0.30 deg/s corresponding to an average improvement of $23 \pm 44\%$. Treatment effects of nGVS were not associated to the degree of vestibular hypofunction as assessed by clinical vestibular function tests. However, the degree of nGVS-induced threshold reductions was correlated with higher baseline perceptual thresholds determined during sham stimulation ($R = -0.791$; $p = 0.007$; Fig. 1C).

Discussion

In this study, we examined the potential therapeutic effects of imperceptible, low-intensity vestibular noise stimulation (i.e., nGVS) on impaired vestibular perceptual capacity in patients with BVP. Vestibular perceptual performance was assessed by means of an established psychophysical two-alternative forced choice paradigm that has been shown excellent test-to-retest reliability [31, 33]. In more than two-third of patients, we observed that application of nGVS effectively lowered vestibular thresholds for the perception of head-centered roll tilt stimuli. In particular those patients with poor vestibular perceptual performance at baseline (i.e., during sham stimulation) notably benefited from nGVS treatment.

The presumed mechanism underlying the observed therapeutic effect is SR [20, 25]. According to this phenomenon, addition of an appropriate amount of noise to a sensory system can effectively lower the system's threshold for signal processing whereas to low or high noise will either not affect or disturb signal transfer [17, 18]. By applying a wide range of nGVS amplitudes (0–0.7 mA) in young healthy individuals, Galvan-Garza and colleagues could previously demonstrate SR-like modulations of vestibular perception with optimal enhancements at intermediate nGVS intensities (0.3–0.5 mA) in 78% of the examined individuals [25]. The present observations in patients with BVP closely correspond to this previous report, both in terms of the rate of responders (73% vs. 78%) and the overall magnitude of response (23% vs. 25% improvement). Such SR-like enhancements of perceptual capacity are not limited to the vestibular system, but have been previously analogously demonstrated for human visual [34], auditory [35], and tactile perception [36].

BVP has been consistently associated with pathologically increased vestibular perceptual thresholds for the registration of translational and rotational motion stimuli [32, 37–39]. Compared to previously reported perceptual thresholds for roll tilt motion in healthy individuals in their sixth decade of life (mean: 1.19 deg/s; 95% CI 1.00–1.42 deg/s [40]), baseline perceptual thresholds in our cohort of patients (mean: 1.67 deg/s; 95% CI 0.92–2.42 deg/s) were in average increased by 40%. Impaired vestibular perceptual performance has been suggested to contribute to a variety of motor and non-motor symptoms associated with BVP [41]. Accordingly, vestibular contributions to balance control are not confined to vestibulospinal reflex control of upright posture but also involve perceptual registration of head and body orientation in space [42, 43]. In the elderly, increased roll tilt perceptual thresholds have been associated to deficits of balance control while standing with eyes closed on compliant support surface [40, 44]—a condition that specifically challenges vestibular balance regulation. The present and previous research in patients with BVP suggests that treatment with nGVS simultaneously targets the vestibular perceptual and the vestibulospinal reflex level [19] and both effects presumably contribute to the reported stabilizing effect of nGVS on static and dynamic balance in BVP [21–24].

Beyond imbalance, there is a range of non-motor symptoms associated with BVP that might specifically benefit from nGVS-induced improvements of vestibular perceptual capacity. The impaired monitoring of head-in-space

orientation and motion in BVP is typically accompanied by specific impairments of navigation, spatial learning and memory as examined in virtual [5, 45] and real space [7] navigation tests. These deficits extend to limitations in patient's activities of daily living in terms of frequent experiences of spatial disorientation, misjudgments of distances, and an increased spatial anxiety [6, 45]. It is conceivable that a sensitization of vestibular perception by nGVS might specifically ameliorate deficits of spatial memory, orientation, and navigation in BVP. In line with this assumption, a previous study could demonstrate nGVS-induced enhancements of spatial memory during a virtual navigation task in young healthy adults [46]. Further studies using virtual and/or real space test paradigms of navigation are, however, required to explore to potential impact of nGVS treatment on deficits of spatial memory and navigation in patients with BVP.

Certain limitations of this study have to be considered. Due to the lengthy procedure of the psychophysical examination and in accordance to previous studies [26–28], we did not examine stimulation effects on vestibular perceptual performance across a range of varying nGVS levels but only tested one nGVS intensity that was individually determined beforehand using a posturographic task. It is conceivable that nGVS intensities that optimally stabilize static posture may more or less differ from those that have the greatest benefit on vestibular motion perception [28]. Hence, an evaluation of different nGVS levels on perceptual performance may have resulted in an even higher rate of responders and magnitude of response as currently observed. Secondly, we only evaluated stimulation effects on one axis of motion, i.e., head-centered rotation in the roll plane. In accordance to previous studies, we specifically focused on perceptual performance along this axis since it involves the integration of sensory cues from both vestibular endorgan structures (semicircular canals and otoliths) [29] and is closely linked to balance performance [40, 44]. Due to the non-specific nature of the nGVS stimulus, we would expect analogous benefits of nGVS on perceptual performance along other axis of motion. However, future studies in patients with BVP are required to verify this assumption—in particular for perceptual performance in the horizontal plane that is essential for spatial orientation and navigation [47]. Finally, while our psychophysical paradigm focused on the perception of vertical canal and otolith cues, clinical evaluation of vestibular hypofunction was primarily based on horizontal canal function. This discrepancy might hence explain the lack of observed association of nGVS treatment effects on roll tilt perceptual thresholds and clinical measures of vestibular hypofunction.

In conclusion, we provide evidence that non-invasive and imperceptible vestibular noise stimulation is effective in improving impaired vestibular perceptual performance in patients with BVP, in particular in those patients with poor baseline perceptual performance. Future studies are required to explore further behavioral consequences of this therapeutic effect, in particular with respect to BVP-related deficits of spatial memory and navigation.

Acknowledgements The study was supported by the German Federal Ministry for Education and Science (BMBF, IFB 01EO1401).

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The ethics committee of the medical faculty of the University of Munich approved the study protocol, which was conducted in conformity with the Declaration of Helsinki.

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Anhang: Paper III

Mechanisms underlying treatment effects of vestibular noise stimulation on postural instability in patients with bilateral vestibulopathy

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Journal of Neurology (2024) 271:1408-1415

doi: 10.1007/s00415-023-12085-3

Journal of Neurology
https://doi.org/10.1007/s00415-023-12085-3

ORIGINAL COMMUNICATION

Mechanisms underlying treatment effects of vestibular noise stimulation on postural instability in patients with bilateral vestibulopathy

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Received: 4 September 2023 / Revised: 26 October 2023 / Accepted: 27 October 2023

Abstract

Background Previous studies indicate that imbalance in patients with bilateral vestibulopathy (BVP) may be reduced by treatment with low-intensity noisy galvanic vestibular stimulation (nGVS).

Objective To elucidate the potential mechanisms underlying this therapeutic effect. In particular, we determined whether nGVS-induced balance improvements in patients are compatible with stochastic resonance (SR)—a mechanism by which weak noise stimulation can paradoxically enhance sensory signal processing.

Methods Effects of nGVS of varying intensities (0–0.7 mA) on body sway were examined in 19 patients with BVP standing with eye closed on a posturographic force plate. We assumed a bell-shaped response curve with maximal sway reductions at intermediate nGVS intensities to be indicative of SR. An established SR curve model was fitted on individual patient outcomes, and three experienced human raters had to judge whether responses to nGVS were consistent with the exhibition of SR.

Results nGVS-induced reductions of body sway compatible with SR were found in 12 patients (63%) with optimal improvements of 31 ± 21%. In 10 patients (53%), nGVS-induced sway reductions exceeded the minimally important clinical difference (optimal improvement: 35 ± 21%), indicative of strong SR. This beneficial effect was more likely in patients with severe vestibular loss (i.e. lower video head impulse test gain; $R = 0.663$; $p = 0.002$) and considerable postural imbalance (baseline body sway; $R = 0.616$; $p = 0.005$).

Conclusions More than half of the assessed patients showed robust improvements in postural balance compatible with SR when treated with nGVS. In particular, patients with a higher burden of disease may benefit from the non-invasive and well-tolerated treatment with nGVS.

Keywords Bilateral vestibulopathy · Galvanic vestibular stimulation · Stochastic resonance · Balance · Body sway

Introduction

Chronic postural instability during standing and walking, which aggravates in darkness and on uneven ground, is a cardinal symptom in patients with bilateral vestibulopathy (BVP) [1–3]. Postural deficits may partially ameliorate as patients adapt behavioural strategies that recalibrate multisensory balance and locomotion control [4–6]. However, deficits typically do not dissipate over time [4, 7], which often results in long-term functional impairment and puts patients at an increased risk for recurrent falling [8, 9].

Therapy of postural deficits in BVP is currently primarily based on vestibular rehabilitation that facilitates behavioural adaptions to chronic vestibular hypofunction [6, 10, 11]. However, treatment by physical therapy yields, if any, only partial compensation for lost vestibular feedback [12]. Patients who cannot compensate centrally via vestibular rehabilitation may in the future benefit from the implantation of a vestibular prosthesis, which has shown first promising effects on postural and other BVP-related symptoms in selected patients [13, 14]. However, benefits of an invasive

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Published online: 16 November 2023

vestibular implant have to be weighed against the risks and cost associated to surgery.

Based on the fact that a majority of patients with BVP retain residual vestibular excitability and function [15, 16], attempts have been made to augment residual vestibular excitability of patients by means of a non-invasive, low-intensity noise stimulation of the vestibular endorgans using noisy galvanic vestibular stimulation (nGVS) [17–19]. Treatment with nGVS has been shown to not only facilitate residual vestibular perceptual and sensorimotor function in patients with BVP [20, 21] but to also stabilise their impaired balance capability during static and dynamic postural tasks [18, 22–26]. As of now, the underlying mode of action of nGVS therapy in patients with BVP is poorly understood. Furthermore, as previous studies consistently observed that not all patients equally respond to stimulation and show a clinically meaningful improvement under treatment [18, 20–26], patient-related factors that may promote or prevent individual treatment success have to be elucidated.

To overcome these deficits, the current study examined individual treatment effects of nGVS on static postural stability in patients with BVP across a broad range of stimulation intensities. In accordance to previous studies, we hypothesised that nGVS modulates vestibular balance function by means of stochastic resonance (SR)—a phenomenon according to which (pathologically increased) thresholds for sensory information processing can be lowered by application of an appropriate amount of low-intensity sensory noise [27, 28]. Exhibition of SR is typically characterised by a noise-induced modulation of the system's output that follows a bell-shaped performance curve with increasing noise intensity, which peaks at a specific intermediate level of noise intensity that optimally facilitates signal transfer within the system. We applied different previously established quantitative and qualitative criteria [29–32] to determine on an individual patient level whether nGVS-induced modulations in balance of patients with BVP are compatible with the exhibition of SR (i.e. display a bell-shaped response curve) or follow other response dynamics. We further examined whether disease-related (aetiology, severity of symptoms, etc.) or demographic factors (age, gender, etc.) may be related to the presence or the absence of treatment responses in individual patients.

Materials and methods

Participants

Nineteen patients with BVP (age 59.9 ± 15.4 years, 9 females) participated in the study and provided written informed consent prior to inclusion. Detailed patient characteristics are provided in Table 1. All patients showed a clinically proven deficit, i.e. a bilateral pathological video head impulse test (vHIT, horizontal gain < 0.6) and/or bilateral reduced or absent caloric responses (sum of maximal peak velocities of the slow-phase nystagmus with cold and warm water < 6 °/s) [33]. Fifteen age-matched healthy controls (age 57.7 ± 4.7 years, 7 females) were included in the study to establish normative data. All participants gave written informed consent prior to study inclusion.

Galvanic vestibular stimulation

Vestibular noise stimulation (i.e. nGVS) was applied via a pair of 4.0 cm × 6.0 cm Ag–AgCl electrodes attached bilaterally over the left and right mastoid process. Zero-mean Gaussian white noise stimulation with a frequency range of 0–30 Hz and varying peak amplitudes of 0–0.7 mA was delivered by a mobile constant current stimulator (neuroConn®, Illmenau, Germany).

Experimental procedures

Body sway was recorded for 30 s on a posturographic force plate (Kistler, 9261A, Kistler Group, Winterthur, Switzerland) at 40 Hz whilst patients were standing with their eyes closed (Fig. 1A). This procedure was repeated eight times, whilst patients were stimulated with a different amplitude of nGVS (ranging from 0 to 0.7 mA, in a randomised order) in each trial. Patients were blinded to the exact stimulation order. Between trials, patients were given a short break to recover.

Data and statistical analysis

For each stance trial, mean sway velocity was calculated as the primary output measure based on the recorded radial centre-of-pressure (CoP) trajectory using the formula $SV = 1/T \times \sum_i |r_{i+1} - r_i|$, [mm/s], where T is the total trial duration (i.e. 30 s) and r_i is the radial CoP distance of the *ith* sample. For further analysis, sway velocity measures from 8 stance trials were normalised to sway velocity obtained during 0 mA stimulation (i.e. baseline condition).

To determine whether SR-like dynamics were present in the balance responses of patients to varying nGVS levels, we tested three increasingly rigorous criteria built on one another: (1) The first criterion tested whether body sway of patients improved for at least one particular nGVS level compared to baseline condition (i.e. 0 mA nGVS). (2) The second criterion was based on a visual inspection of response dynamics of body sway across increasing nGVS level by three experienced human raters (i.e. MW, JE, and KJ). Each rater had to evaluate whether (in addition to the fulfilment of the first criterion) nGVS-amplitude-dependent changes of body sway in individual patients were further

Table 1 Clinical characteristics and global stimulation effects of patients

Patient	Sex	Age	Aetiology	Caloric response, deg/s[a]		vHIT gain		Optimal nGVS, mA	Exhibition of SR
				Left	Right	Left	Right		
P1	M	62	Idiopathic	–	–	0.33	0.58	0.2	Weak
P2	F	50	Idiopathic	4.4	1.3	0.18	0.16	0.1	Strong
P3	M	82	Idiopathic	2.3	1.3	0.50	0.26	0.5	Strong
P4	M	37	Idiopathic	13.9	2.8	0.53	0.15	-	None
P5	F	82	Infectious	8.9	21.1	0.51	0.56	–	None
P6	M	62	Idiopathic	–	–	0.64	0.56	0.3	Weak
P7	F	65	Idiopathic	3.8	1.1	0.66	0.34	–	None
P8	F	32	Autoimmune	4.0	1.5	0.15	0.27	0.3	Strong
P9	F	69	Neuro-degenerative	5.0	3.5	0.29	0.58	0.5	Strong
P10	M	61	Neuro-degenerative	0.9	0.4	0.00	0.02	0.1	Strong
P11	M	58	Idiopathic	13.6	4.9	0.26	0.57	0.3	Strong
P12	F	81	Idiopathic	5.5	3.9	0.45	0.56	0.7	None
P13	F	54	Neuro-degenerative	3.6	2.3	0.22	0.15	0.4	Strong
P14	M	69	Ototoxic	–	–	0.39	0.54	0.7	None
P15	M	53	Idiopathic	6.9	1.0	0.73	0.78	–	None
P16	M	60	Ototoxic	3.0	2.0	0.10	0.10	0.4	Strong
P17	F	28	Autoimmune	0.9	0.9	0.27	0.47	0.4	Strong
P18	M	72	Ototoxic	1.2	0.8	0.28	0.33	0.7	None
P19	F	61	Idiopathic	4.2	1.4	0.30	0.17	0.1	Strong

vHIT video head impulse test, *nGVS* noisy galvanic vestibular stimulation

[a]Sum of maximal slow-phase eye velocity during warm and cold caloric irrigation

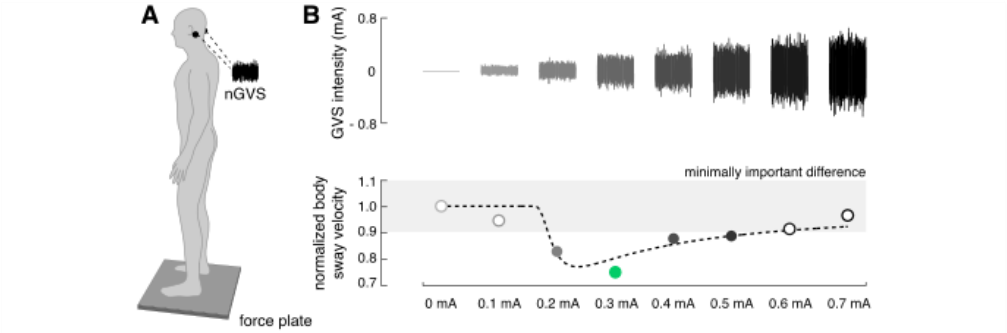
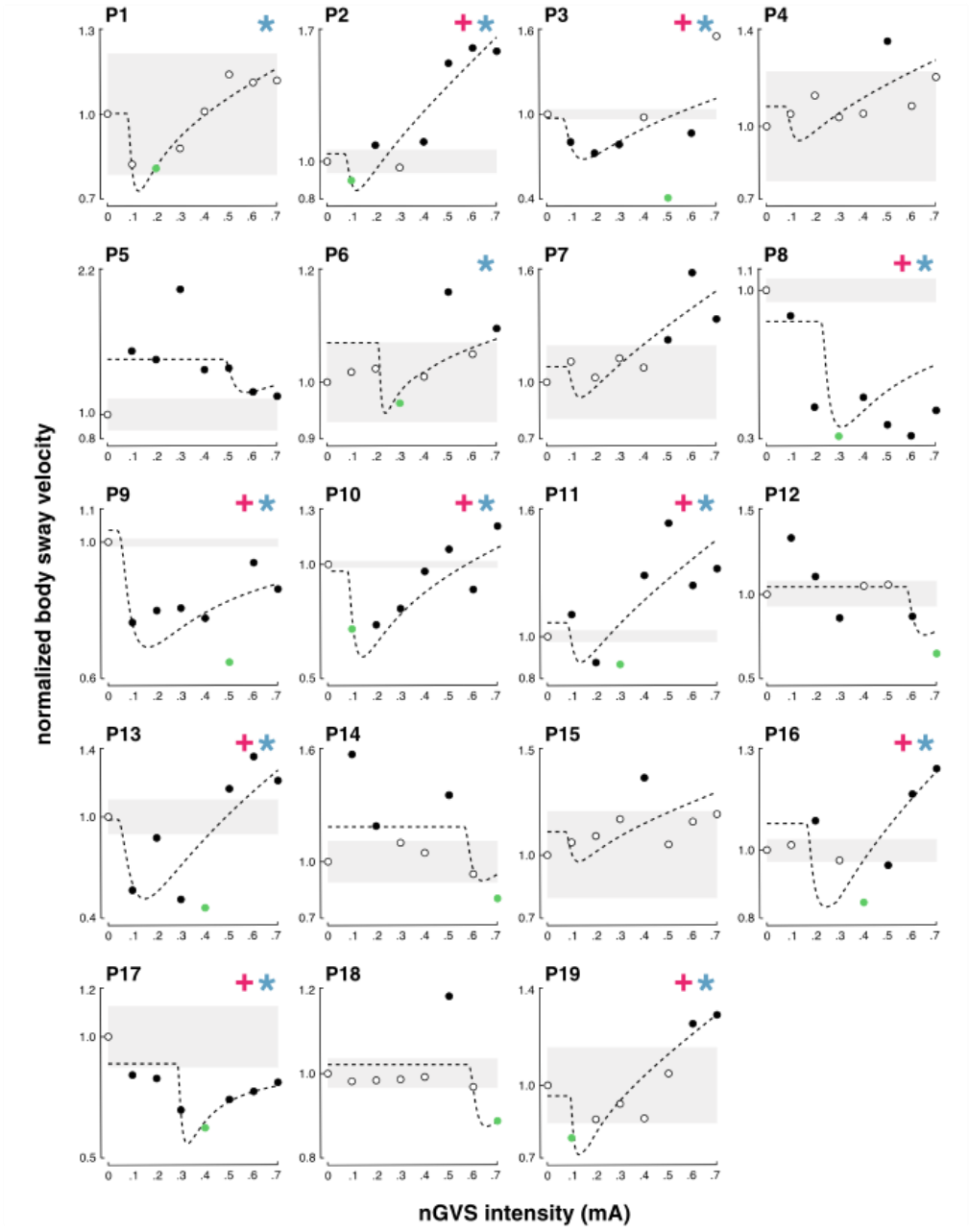


Fig. 1 Experimental setup and procedures. **A** Effects of noisy galvanic vestibular stimulation (nGVS) on static balance in patients were measured on a posturographic force plate. Velocity of body sway was calculated from the resultant center-of-pressure trajectories. **B** Exemplary modulation of body sway (simulated data, lower panel) across the administered nGVS intensities (upper panel) that follows a bell-shaped performance curve indicative of the presence of stochastic resonance (model fit: dashed line). Filled dots indicate body sway reductions greater than the minimally important difference (grey area). The green filled dot indicates the optimal reduction of body sway at a particular nGVS level

compatible with a bell-shaped response curve with improvements of performance at intermediate stimulation intensities that is indicative of the presence of SR. For this evaluation, each rater was independently provided with a plot of the normalised nGVS-dependent changes in body sway and a superimposed theoretical SR curve that was fit on the data using a goodness-of-fit statistics [29, 30] (see example Fig. 1B). The applied equation fit represents an adapted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normalized body sway velocity
nGVS intensity (mA)

◂**Fig. 2** Individual effects of low-intensity vestibular noise stimulation on static balance. Normalised body sway responses to noisy galvanic vestibular stimulation (nGVS) are plotted against the administered nGVS levels for each individual patient. Dashed lines represent the stochastic resonance (SR) model fits. Black filled dots indicate body sway modulations greater than the minimally important clinical difference (grey area). Green filled dots indicate optimal reductions of body sway at particular nGVS levels. Blue asterisks denote those patients that exhibit SR-like responses according to three human judges (weak SR). Pink crosses denote those patients that additionally show clinically meaningful improvement of body sway (strong SR)

version of the originally proposed SR model by Benzi [34], including a piecewise, linear masking effect to model cases where nGVS effects at high amplitudes may have detrimental effects on the performance metric [35]. The criterion was met if at least two of the raters identified the presence of SR-like dynamics. (3) The third criterion additionally evaluated whether improvements at intermediate nGVS levels were greater than the minimal clinically important difference (MCID; defined as half the standard deviation for normative data [36]) for changes in body sway velocity. MCID for sway velocity was 2.3 mm/s calculated based on the posturographic recordings of the 15 age-matched healthy individuals standing with eyes closed for 30 s.

Based on the three criteria, patients were classified as showing solely optimal improvement and no SR (criterion 1), exhibiting weak SR (criteria 1 & 2) or showing strong SR (criterion 1, 2, & 3). Potential correlations between SR classification and age, gender, aetiology, vHIT gain, caloric response, and baseline body sway were analysed using Spearman's rank correlation. Results were considered significant at $p < 0.05$. Statistical analysis was performed using SPSS (Version 26.0, IBM Corp., USA).

Results

Application of nGVS at intensities ranging from 0.1 to 0.7 mA was well tolerated and did not cause apparent disequilibrium in any of the examined patients. In the first step of analysis, we evaluated whether body sway velocity was decreased by at least one particular nGVS intensity compared to sham stimulation (i.e. nGVS at 0 mA). This criterion was met by 15 patients (79%) with an optimal improvement magnitude of in average 29% (range 4–69%) at an average intensity of 0.4 mA (range: 0.1–0.7 mA).

In the second step, an established SR model was fit to the individual modulations of body sway velocity in dependence of nGVS intensity (Fig. 2). Three experts were asked to independently rate for each patient by visual inspection of individual sway velocity modulations and corresponding model fits whether body sway responses follow a bell-shaped performance curve or not. Based on their judgments, SR-like treatment responses to nGVS were present in 12 patients (63%) with optimal improvements of 31% (range 4–69%) at an average intensity of 0.3 mA (range: 0.1–0.5 mA). Analogous bell-shaped performance modulations with optimal improvement at intermediate noise intensities were found on the group average response level of these patients (Fig. 3). In the remaining patients (37%), body sway velocity either randomly fluctuated (3 patients) or was generally increased (4 patients) across the range of tested nGVS intensities.

We subsequently identified those patients that in addition to SR-like response dynamics showed a clinically meaningful improvement of static balance (i.e. a reduction of body sway velocity greater than the MCID, Fig. 2). This criterion for the exhibition of strong SR was met by 10 patients (53%) with an average optimal improvement of 35% (range 10–69%) at an average intensity of 0.3 mA (range: 0.1–0.5 mA). Considerable SR-like performance improvements were also apparent on the group average level of patients exhibiting strong SR (Fig. 3).

In the final step, we explored demographic and disease-related factors that may potentially promote or hamper the exhibition of weak or strong SR in response to nGVS treatment. Correlation analysis revealed a positive association between baseline levels of static body sway (i.e. sway velocity assessed during nGVS at 0 mA; $R = 0.616$; $p = 0.005$) and a negative association with the vHIT gain assessed during clinical examination ($R = -0.663$; $p = 0.002$). Hence, patients with profound postural impairments at baseline and a significant vestibulo-ocular reflex deficit were more likely to exhibit SR-like balance improvements at clinically meaningful effects sizes under treatment with nGVS.

Discussion

There is increasing evidence that postural symptoms in patients with BVP may ameliorate in response to a non-invasive, low-intensity noise stimulation of the vestibular endorgans (i.e. nGVS) [18, 22–26]. Albeit the mode of action underlying this treatment effect was repeatedly attributed to SR in vestibular sensorimotor and/or perceptual pathways, previous studies failed to provide sufficient evidence for the latter assumption. The reason for this is that these studies typically limited the application and/or analysis of treatment outcomes to one particular noise intensity and could thus not determine whether postural responses follow a SR-like bell-shaped response curve with increasing noise intensity. Since a better understanding of the treatment principle underlying nGVS is important for future therapeutic applications, we here explicitly evaluated nGVS treatment effects to nGVS across a broad range of noise intensities to determine (1) whether nGVS-induced modulations of postural imbalance in individual patients are compatible with the exhibition of

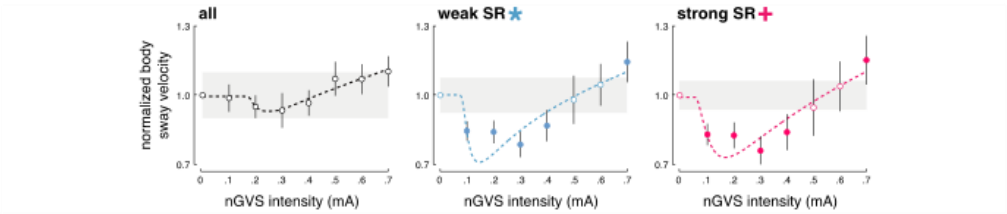

Fig. 3 Group average effects of low-intensity vestibular noise stimulation on static balance. Group average normalised body sway responses (mean ± SEM) to noisy galvanic vestibular stimulation (nGVS) are plotted for each of the administered nGVS levels for all patients (left panel), those patients exhibiting weak stochastic resonance (SR; middle panel), and those exhibiting strong SR (right panel). Filled dots indicate body sway modulations greater than the minimally important clinical difference (grey area)

SR and to further identify (2) demographic and/or disease-related factors that may qualify patients to particularly benefit from treatment with nGVS.

Our analysis revealed that postural responses in about two thirds of patients closely followed a bell-shape performance curve with optimal balance improvements at intermediate noise intensities—a response rate that is considerably higher than previously reported in young healthy individuals where nGVS-induced balance responses compatible with SR were only rarely observed [30]. Static balance of patients was optimally stabilised at an average intensity of 0.3 mA (range: 0.1 to 0.5 mA), which is compatible to previous reports on nGVS-induced SR in healthy individuals and other clinical cohorts [29, 31] and approximates 60% of the estimated detection threshold of vestibular afferent responses to GVS [37]. We further found that at least half of the patients showed nGVS-induced balance improvements at clinically meaningful effect sizes. In the remaining third of patients, nGVS-induced balance responses did not exhibit SR-like response dynamics. In some of these, balance responses did not show any systematic dependency on nGVS and thus likely reflect variations in the performance metric (i.e. body sway) rather than any therapeutic effect. In others, nGVS treatment degraded balance performance irrespective of stimulation intensity, which might indicate a general intolerance to low-intensity vestibular noise stimulation.

We further explored potential demographic and/or disease-related factors that may influence nGVS treatment response in individual patients. We found that the integrity of vestibulospinal and vestibulo-ocular reflex function was associated with the presence or absence of stimulation benefits. Accordingly, patients with greater postural instability during visual withdrawal—a proxy for impairment of vestibular (and proprioceptive) balance regulation—were more likely to exhibit SR-like balance improvements at clinically meaningful effects sizes under treatment with nGVS. Analogously, we found that patients with a lower gain during vHIT assessment—a proxy for the impairment of vestibulo-ocular reflex function—showed greater benefits from nGVS treatment. This suggests that patients with residual but severely compromised peripheral vestibular function may particularly benefit from treatment with low-intensity vestibular noise stimulation. Similar associations between nGVS treatment response and the capacity or integrity of vestibular function were found in young and healthy elderly adults [38, 39].

Taken together with previous evidence from studies in vestibular animal models and humans, the current results shed light on the presumable mode of action underlying nGVS treatment effects on static balance. Previous studies in frog and chicken demonstrated that low-intensity noise exerted on the vestibular endorgans induces SR-like improvements of vestibular signal transfer at the level of vestibular hair cells and primary vestibular afferents [40, 41]. Subsequent studies in humans indicate that noise-induced improvements in signal processing at the vestibular periphery are conveyed to centrally mediated vestibulospinal and vestibular perceptual functions. Accordingly, both healthy individuals and patients with BVP exhibit a SR-like sensitisation of vestibular motion perception in response to nGVS treatment [21, 29, 42, 43]. Analogously, nGVS was shown to induce SR-like enhancement of vestibulospinal responses in both cohorts [20, 44]. Both of these effects are likely to contribute to the observed SR-like stabilisation of postural imbalance in patients with BVP. Accordingly, previous evidence indicates that vestibular balance control is not confined to vestibulospinal reflex control but also involves the perceptual registration of head and body in space [45, 46]. Our observations further suggest, that nGVS-induced enhancements at the vestibular reflex and perceptual level only manifest in a clinically meaningful postural stabilisation in individuals with significantly compromised balance performance at baseline.

In conclusion, we found evidence that low-intensity noise stimulation ameliorates postural imbalance in about two thirds of the assessed patients with BVP. In particular, patients with severe impairments of peripheral vestibular

function are likely to show balanced improvements at clinically meaningful effects sizes under treatment. nGVS-induced balance improvements in these patients are further consistent with the exhibition of SR in vestibular sensorimotor and perceptual pathways. Future studies are required to investigate whether nGVS may analogously target other BVP-related impairments in gaze stabilisation and spatial cognition.

Acknowledgements The authors thank Lorenz Assländer for providing recourses for data analysis. The study was supported by the German Federal Ministry for Education and Science (BMBF, 01EO1401 & 13GW0490B).

Funding Open Access funding enabled and organized by Projekt DEAL.

Data availability The datasets used and/or analysed during the current study will be available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest MW and KJ received funding from the neuroConn GmbH (DC stimulator).

Ethical standards The ethics committee of the medical faculty of the University of Munich approved the study protocol, which was conducted in conformity with the Declaration of Helsinki.

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Danksagung

An dieser Stelle möchte ich allen beteiligten Personen danken, die mich bei der Anfertigung meiner Dissertation unterstützt haben.

Zuerst möchte ich mich bei Herrn Prof. Dr. med. Klaus Jahn für die Bereitstellung des Themas und die hervorragende Betreuung während der gesamten Arbeit bedanken. Als mein Doktorvater stand er mir mit Rat und Kritik stets zur Seite.

Auch bei Herrn PD Dr. rer. nat. Max Wühr bedanke ich mich herzlich für die großartige Unterstützung bei der Umsetzung der gesamten Arbeit. Vor allem bei technischen und statistischen Fragen hatte er immer ein offenes Ohr.

Ein großer Dank geht an Silvy Kellerer, die die erstklassige physiotherapeutische Behandlung der Patienten übernahm und mich auf meinem Weg mit lieben Worten begleitet hat.

Außerdem bedanke ich mich bei dem gesamten Team der Schwindelambulanz für die gute Zusammenarbeit. Dazu zählen auch die ehemaligen Mitarbeiter Prof. Dr. med. Julia Dlugaizcyk, Dr. Aram Keywan und Tamara Amberger, die maßgeblich an dieser Arbeit beteiligt waren.

Besonders hervorheben möchte ich die Teilnehmer der Studien, die das Projekt durch ihren Einsatz und ihre Zeit erst ermöglicht haben. Vielen Dank!

Auch meinem Partner und meinen Freunden, die mich in der Zeit der Entstehung dieser Arbeit immer ermutigt haben, möchte ich meinen Dank ausdrücken.

Als letztes gilt mein Dank meiner Familie, die mir das Studium in dieser Weise ermöglicht und mich stets in meinen Entscheidungen unterstützt hat.