



UNIVERSIDADE CATÓLICA PORTUGUESA

**EVALUATION OF CENTRAL AND PERIPHERAL
VESTIBULAR PATIENTS WITH THE VIDEO-HEAD
IMPULSE TEST**

*A dissertation submitted for the degree of
Doctor in Health Sciences,*

Leonel Almeida Luís

Instituto de Ciências da Saúde

March 2015



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**AVALIAÇÃO DE DOENTES VESTIBULARES DE
ORIGEM CENTRAL E PERIFÉRICA COM O
VÍDEO-HEAD IMPULSE TEST**

*Dissertação submetida para a obtenção do grau de
Doutor em Ciências da Saúde*

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Sob orientação dos Prof. Doutores Alexandre Castro Caldas e João Costa

Instituto de Ciências da Saúde

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Preface

This *thesis* dissertation presents the results of the research that was carried out at the Clinical Translational Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon EMG and Motor Control Unit, Neurology Department, Clínic University Hospital, Barcelona, Spain and at the in close collaboration with the German Centre for Vertigo and Balance Disorders, Munich University Hospital, Germany. The Heads of those departments are Professor Mamede de Carvalho, Professor Josep Valls-Solé, and Professor Thomas Brandt, respectively. The research work was developed between 2011 and 2014, under the supervision of Professor Alexandre Castro Caldas from the Health Sciences Institute, Portuguese Catholic University and Professor João Costa, from the Clinical Translational Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon.

The main objective of this work was to study the functioning of the vestibular system circuitry in humans, by taking the opportunity to perform neurophysiological studies with the video-Head Impulse Test, in normal subjects and patients with acute and chronic peripheral and central vestibular disorders, at a clinical level.

The dissertation is written in English, with an extended summary in Portuguese, as predicted in the *Artigo 10º do Regulamento Geral de Doutoramento da Universidade Católica Portuguesa, parágrafo 2 (Despacho NR-111/98, ao disposto no Decreto-Lei no 74/2006)*. All the results presented in this dissertation are already published, accepted or submitted for publication, as it is also predicted in the *Artigo 10º do Regulamento Geral de Doutoramento da Universidade Católica Portuguesa, parágrafo 4*.

This *thesis* is organized in five main chapters, preceded by an abstract and the extended summary in Portuguese. The first chapter begins with a *General introduction* that presents a general overview of the previous and current research done in this field, followed by a second chapter with the specific *Rational and objectives* of the present work. In the third chapter the *General technical and methodological aspects* that were common to all the experiences carried out are presented. The fourth chapter presents the six main *Clinical studies* carried out, namely in normal subjects, acute vestibular syndrome patients of peripheral and central origin, and particular hereditary neurodegenerative

disorders' patients with and without vestibular system involvement. The fifth and last chapter presents a *General discussion* of the results described in the previous sections and the *Concluding remarks and future perspectives* summarising the most important conclusions and future perspectives for neurophysiological studies in this field. At the end, a list of all the *References* used in this dissertation is presented, as well as an *Appendix* with a list of the publications that resulted from the research carried out, and the institutional *financial support* received throughout the duration of this project.

It wouldn't have been possible to perform this research without the collaboration of many people and institutions, to which I wish to express my gratitude.

I acknowledge my supervisor, Professor Alexandre Castro Caldas, for the opportunity to work on this thesis, for his support and encouragement and for giving me the freedom to pursue my ideas.

I am deeply grateful to Professor João Costa for supporting me in all the stages of this work and for his confidence in my work. I acknowledge his knowledge, patience, generosity, encouragement and support. He has been my mentor and a very dear friend.

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I also acknowledge my colleagues and the technical staff from the Hospital de Santa Maria and Faculdade de Medicina de Lisboa, namely Dr. António Marques Pereira, for their permanent help, support and friendship.

Finally, special thanks to my family and friends for their inspiration, encouragement and love.

To my father, a Ménière's patient, the most likely reason for becoming a medical doctor and to my mother for her unconditional love my eternal gratitude.

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À minha família,

A janela não é como as outras janelas das outras casas. Esta, está dividida em linhas pretas verticais, constantes, que dilaceram a imagem que a cidade oferece. A realidade, assim fatiada, transforma-se numa instalação artística, como se a arte e a vida pudessem encontrar naquele espaço, um novo fôlego para comunicar.

RMP, Caixa de Vidro, 2014

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Video Legends

Video 1. Head impulses normal and slow-motion-video in a normal subject.

With head impulses to both sides, the eyes compensate for the head so that no compensatory refixation saccades are triggered. Note that, for recording purposes, the examiner is holding the subject's head from behind and the subject is looking at the camera instead of at the examiner's nose.

Video 2. Ipsilesional and contralesional head impulses slow-motion-video in a patient with left vestibular neuritis.

- a) *30 days after onset.* With head impulses to the left (lesion side), the eyes do not compensate for the head and the patient makes a compensatory refixation saccade; see figure 5a for the ipsilesional vHIT recording.
- b) *8 months after onset.* Both ipsilesional and contralesional head impulses trigger no overt saccades; see figure 5b for the ipsilesional vHIT recording.

Video 3. Ipsilesional and contralesional head impulses in an acute vestibular syndrome patient with right spontaneous nystagmus after a left superior vestibular neuritis.

With head impulses to the left (lesion side), the eyes do not compensate for the head and the patient makes a compensatory refixation saccade. It may be difficult to distinguish nystagmus quick phases from refixating corrective saccades during ipsilesional impulses since they share the same direction and kinematic characteristics. Video runs at 100 and 25 % of the original speed.

Video 4. Head impulses in an acute vestibular syndrome patient with right spontaneous nystagmus after an acute ischemic lesion in the right middle cerebellar peduncle.

With head impulses to both sides, the eyes compensate for the head. Video runs at 100 and 25 % of the original speed.

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List of abbreviations

AQEM	Anti-compensatory quick eye movement
AVL	Acute Vestibular Lesion
CNS	Central nervous system
AVS	Acute Vestibular Syndrome
BPPV	Benign Paroxysmal Positional Vertigo
BVL	Bilateral Vestibular Lesion
CNS	Central Nervous System
CVL	Chronic Vestibular Lesion
HD	Huntington's Disease
HIT	Head Impulse Test
hVOR	VOR gain along the horizontal semicircular canal plane
MD	Ménière's Disease
MRI	Magnetic resonance imaging
QEM	Quick Eye Movements
SARA	Scale for the Assessment and Rating of Ataxia
SCA	Spinocerebellar ataxia
SCC	Semicircular canal
SN	Spontaneous Nystagmus
UVL	Unilateral Vestibular Lesion
VEMP	Vestibular Evoked Myogenic Potentials
VN	Vestibular Neuritis
vHIT	Video Head Impulse Test
VOR	Vestibulo-Ocular Reflex

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ABSTRACT

Dizziness and vertigo are highly prevalent symptoms that accompany a wide variety of conditions including peripheral vestibular dysfunction, central (vestibular) lesions and somatoform disorders. A correct diagnosis is the prerequisite for successful treatment, which should be directed towards the underlying pathophysiology. Neurophysiological methods that test the integrity of the peripheral and central vestibular system circuitry are essential to make an accurate diagnosis in clinical practice. Currently, that assessment is achieved primarily through eye movement analysis in response to semicircular canal stimulation, namely through caloric stimulation and head impulses. The quantification of the vestibulo-ocular reflex (VOR) dynamic parameters and the characterization of quick eye movements (QEM) triggered with head impulses can now be non-invasively and easily assessed with the video head-impulse test (vHIT). This provided a unique opportunity to carry out neurophysiological studies on the oculomotor responses generated by head impulses in humans.

Our aim was to determine if the involvement of central vestibular pathways caused differential disturbances in VOR dynamic changes when explored with the vHIT, which could contribute not only to the differential diagnosis of patients but also to the understanding of VOR control mechanisms.

We explored normal subjects and patients diagnosed with acute vestibular syndrome with spontaneous nystagmus of peripheral and central origin and hereditary neurodegenerative disorders.

Looking for a simple sign of peripheral disease with the vHIT we noticed anti-compensatory eye movements (AQEM) in patients with peripheral aetiologies of spontaneous nystagmus (SN). In the first study we looked for the accuracy of AQEM to differentiate central from peripheral origins of SN. We recorded the eye movements in response to horizontal head impulses in a group of 43 consecutive patients with acute vestibular syndrome (12 with central, 31 with peripheral disorders), 5 patients after acute vestibular neurectomy (positive controls) and 39 healthy subjects (negative controls). AQEM were defined as quick eye movements (peak velocity above $50^\circ/\text{s}$) in the direction of the head movement. All patients with peripheral disorders and

positive controls had AQEM (latency 231 ± 53 ms, amplitude $3.4\pm 1.4^\circ$, velocity $166\pm 55^\circ$ /s) when their head was moved to the opposite side of the lesion. Central patients did not have AQEM. AQEM occurrence rate was higher in peripheral patients with contralesional ($74\pm 4\%$, mean \pm SD) in comparison to ipsilesional ($1\pm 4\%$) impulses ($p<0.001$). Overall diagnostic accuracy for differentiating central from peripheral patients was 96% (95% CI for AUC ROC curve: 0.90 to 1.0) for VOR gain and 100% (95% CI: 1.0 to 1.0) for AQEM occurrence rate. These results suggest that AQEM are a sign of vestibular imbalance in a peripheral deficit and should be added to VOR gain analysis in acute vestibular syndrome patients.

In the second study on acute vestibular syndrome we reported on a patient with benign paroxysmal positional vertigo (BPPV) and spontaneous nystagmus due to otoconia causing a plug in the horizontal semicircular canal. The video head-impulse test revealed an eye velocity saturation with ipsilesional head impulses that normalized after liberatory maneuvers, documenting for the first time a reversible deficiency of the cupular-endolymph high-frequency system dynamics. Furthermore cervical and ocular vestibular myogenic potentials were absent during stimulation of the affected side before the liberatory maneuvers, but normalized within 30 to 80 days. These observations challenge the common belief that VEMPs are evoked by otolith stimulation only, as the assumption of a reversible canal dysfunction by a plug offers a more plausible explanation for all effects.

Finally, we reported on a patient presenting with a one-year history of progressive unsteadiness, particularly when in darkness. The video-Head Impulse Test (vHIT)¹ (Figure 1 B) revealed a significantly reduced vestibulo-ocular reflex (VOR) gain in both horizontal (0.38 ± 0.07 and 0.29 ± 0.05) and posterior canals (0.49 ± 0.05 and 0.38 ± 0.06) with covert and overt corrective saccades, but normal VOR responses in both anterior canals (0.89 ± 0.08 and 1.04 ± 0.15), for right and left impulses, respectively. No plausible combination of end-organ lesion should be responsible for these observations. A brain MRI disclosed a left inferior cerebellar peduncle lesion suggestive of a glioma. To the best of our knowledge, this is the first report where three-dimensional vHIT, by means of peripheral-unlikely combinations of VOR lesion, has shown to be of topodiagnostic value.

In the second set of studies we explored patients diagnosed with hereditary neurodegenerative disorders with and without vestibular system

involvement. In the first study we explored 18 genetically confirmed Huntington's disease patients (44.7 ± 8.1 years; male=9). VOR latency, VOR gain and QEM characteristics were not different from controls ($p > 0.11$ for all comparisons), suggesting that VOR is preserved at physiological frequency domains in these patients, even in more advanced stages of the disease.

In the final study we explored 23 patients with a clinical and genetically confirmed diagnosis of spinocerebellar ataxia (SCA) type 3 ($n=15$), type 2 ($n=4$) and type 1 ($n=4$), and 9 patients with early onset Friedreich's ataxia (FA). VOR latency was higher in FA ($p < 0.001$) and SCA3 ($p = 0.02$) as compared to controls, discriminating FA from other ataxic patients with an overall diagnostic accuracy of 88%. VOR_r , VOR_{40} and VOR_{60} were significantly lower in FA and SCA3 ($p < 0.01$). VOR_{80} was only significantly lower than controls in SCA3 ($p < 0.01$), discriminating these from other ataxic patients with an overall diagnostic accuracy of 78%. Covert saccades were only triggered in SCA3 but with low occurrence rate and peak velocity ($11.1 \pm 28.5\%$ and $77.50 \pm 15.30^\circ/s$) whereas overt saccades were present in all groups. VOR_r gain showed a negative correlation with disease severity evaluated with SARA (Spearman $r = -0.46$, $p = 0.01$). vHIT provides phenotypic information that differentiates the most common autosomal ataxias and can serve as a strategy to orient genetic diagnosis. A correlation between VOR and SARA raises the possibility of using VOR gain as a neurophysiologic biomarker for disease severity.

Altogether these results supply relevant data in distinguishing peripheral and central nervous system (CNS) vestibular deficits, particularly acute deficits in emergency situation, as acute CNS vertigo can be life-threatening (stroke) and require immediate medical action. We first demonstrated that not only VOR instantaneous gain analysis has topodiagnostic value but also the analysis of gain dynamic changes, as these can point to individual aetiologies, e.g. a SCC plug. Secondly we demonstrated that quick eye movements also supply topodiagnostic cues, and should have their latency, peak velocity, direction and occurrence rate analysed.

At a neurophysiological level, the oculomotor responses generated by head impulses also provide an understanding of both the biomechanical cupular-endolymph dynamics, the VOR dynamic control processes taking place and the modulation of vestibular spontaneous nystagmus with head impulses

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RESUMO

Introdução

A vertigem e a tontura são sintomas muito prevalentes que acompanham uma grande variedade de patologias, nomeadamente as vestibulopatias periféricas, centrais e as perturbações somatoformes. Um diagnóstico correcto é o pré-requisito para um tratamento eficaz, o qual deverá ser dirigido à patofisiologia de base. Os métodos neurofisiológicos que testam a integridade dos circuitos do sistema vestibular central e periférico são essenciais para alcançar um diagnóstico preciso na prática clínica. Actualmente, essa avaliação é realizada principalmente pela análise dos movimentos oculares originados pela estimulação dos canais semicirculares, nomeadamente a estimulação calórica e os impulsos cefálicos. A quantificação dos parâmetros dinâmicos do reflexo vestibulo-oculomotor (VOR) bem como a caracterização dos movimentos oculares rápidos (QEM, Quick Eye Movements) desencadeados com os impulsos cefálicos podem agora ser avaliados de forma fácil e não-invasiva com o vídeo Head Impulse Test (vHIT). Tal proporciona a oportunidade única de promover estudos neurofisiológicos das respostas oculomotoras desencadeadas pelos impulsos cefálicos em humanos.

Acelerações horizontais da cabeça geram, na obscuridade, movimentos oculares conjugados lentos e compensatórios na direção oposta, sendo este reflexo denominado VOR. O principal objetivo deste reflexo é a manutenção de visão nítida e clara por estabilização da imagem na retina, principalmente durante os movimentos rápidos da cabeça. O Head Impulse Test (HIT)¹ ou teste de impulsão cefálica é um teste clínico ativo em que este VOR angular é testado a alta frequência. O clínico, ao colocar-se de frente para o doente, aplica movimentos de frequência e direção imprevisíveis segundo o plano horizontal, de baixa amplitude (10-25°), alta aceleração (3.000-6.000°/s²) e velocidade (150-300°/s), enquanto o doente é instruído a manter a fixação num ponto. Se o VOR estiver intacto, o doente será capaz de manter a fixação, não se observando qualquer movimento rápido do olho, denominando-se o HIT de normal ou negativo. Pelo contrário, se o VOR não for compensatório, o olho acompanhará a cabeça durante a rotação impulsiva pelo que no final do impulso será necessário realizar uma sacada de refixação para recolocar o alvo

¹ Halmagyi GM, Curthoys IS, Cremer PD, et al. The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation before and after unilateral vestibular neurectomy. *Exp Brain Res.* 1990;81(3):479-90.

na fóvea, denominando-se o HIT de positivo ou patológico. Dado que não é possível ao olho humano detectar o movimento de fase lenta do VOR durante este impulso, a presença de uma sacada compensatória no final de um HIT clínico é entendida como um sinal indireto de uma fase lenta não compensatória.

Enquanto o HIT unicamente permite a identificação da presença de sacadas após o impulso cefálico, o vídeo HIT (vHIT)² possibilita não só a identificação e a quantificação da fase lenta do VOR, como também das fases rápidas geradas durante e após o impulso cefálico. Indivíduos saudáveis geram fases lentas compensatórias de baixa latência (7-10 ms), gerando fases rápidas ocasionais após os impulsos. Pelo contrário, doentes com lesão vestibular unilateral (UVL) desencadeiam fases lentas com latência aumentada, não-compensatórias durante impulsos ipsilesionais, assim como movimentos oculares rápidos durante ou após os mesmos. Estes movimentos rápidos são conhecidos como sacadas *covert* se desencadeadas durante o impulso cefálico, dado a sua observação não ser possível a olho nu, ou como sacadas *overt* se desencadeadas após o impulso cefálico. Dado que estas fases rápidas apresentam o mesmo sentido da fase lenta deficitária, diminuindo o erro ocular, são consideradas sacadas compensatórias. Os doentes UVL agudos também podem gerar fases lentas não compensatórias durante os impulsos contralesionais, resultado da lesão da via inibitória ipsilesional, bem como gerar fases rápidas.

A quantificação do HIT por vídeo-oculografia permite aumentar substancialmente a sensibilidade e a especificidade do HIT na avaliação do VOR sem as dificuldades técnicas dos coils, de difícil utilização na prática clínica. As novas câmaras digitais apresentam características de peso, forma, resolução espacial e de taxa de amostragem que permitem a sua utilização na prática clínica na quantificação do HIT com boas taxas de correlação com o *coil*.

O registo dos perfis de velocidades ocular e cefálica durante o impulso cefálico permite o cálculo do ganho do VOR, definido como o *ratio* entre estas velocidades. Esse *ratio* pode ser calculado em momentos específicos, como p.ex. a 40, 60 e 80 ms após início do impulso (ganho instantâneo) ou como resultante de regressão linear (ganho por regressão). Enquanto que o último

² Bartl K, Lehnen N, Kohlbecher S, Schneider E. Head Impulse Testing Using Video-oculography. Ann N Y Acad Sci. 2009;1164(1):331-3.

parece ser o valor mais robusto, o primeiro permite a avaliação variação dinâmica do ganho do VOR durante o impulso. Para o cálculo do VOR contribui a sua latência, de tal forma que se esta fosse zero deveríamos ter valores de ganho de 1.0. Dada a existência de uma latência e, portanto, de uma discrepância entre as curvas de velocidades cefálica e ocular, os valores de normalização que obtivemos no nosso laboratório são ligeiramente inferiores (0.95 ± 0.09). Calculando os limites de normalidade do ganho de VOR, obtivemos valores de 0.77 a 1.13. A avaliação do ganho de VOR permite por último o cálculo da assimetria interaural, que apresenta nas nossas séries, valores de normalidade muito baixos ($<6.97\%$), quando comparados com os valores de normalidade para as provas calóricas ($<25\%$).

Os QEM são identificados como picos de aceleração bidirecionais e são classificados de acordo com o sentido relativo à fase lenta, a latência (ms), o pico de velocidade ($^{\circ}/s$) e a taxa de ocorrência ($\%$, taxa de impulsos que geram esses QEM). Os QEM podem apresentar o sentido da fase lenta do VOR deficitário e contribuir para a diminuição do erro ocular, sendo consideradas sacadas de correção ou sacadas *catch-up*, em analogia com os QEM da perseguição sacádica. Nas situações em que o ganho do VOR apresenta valores superiores à normalidade (situação observada em doentes com algumas patologias centrais) podem assumir o sentido contrário ao da fase lenta do VOR e ser igualmente classificadas como sacadas de correção uma vez que trazem a retina de regresso ao alvo. Nos indivíduos normais por nós estudados as sacadas *overt* apresentam valores de velocidade e de taxa de ocorrência relativamente baixos, enquanto as sacadas *covert* são inexistentes.

Assim, a existência de uma lesão vestibular aguda (UVL) é verificável através do vHIT pela presença de uma fase lenta não compensatória durante os impulsos ipsilesionais. O cálculo do ganho do VOR e do índice de assimetria, permitem quantificar o grau da lesão. Nas fase aguda da lesão, o erro ocular resultante de um menor ganho de VOR é mais elevado, pelo que são identificadas sacadas compensatórias mais frequentes, com maior velocidade de pico e maior amplitude, tanto durante como após o impulso ipsilesional. Pelo contrário, durante a recuperação da fase lenta verifica-se o aumento progressivo da latência e diminuição da taxa de ocorrência destas sacadas.

A maior parte dos doentes com síndrome vestibular agudo³, definido como vertigem espontânea com nistagmo espontâneo, náuseas, vômitos e

³ Hotson JR, Baloh RW. Acute vestibular syndrome. N Engl J Med. 1998;339(10):680-5.

desequilíbrio, resultam de lesão vestibular unilateral aguda. No entanto, a identificação no serviço de urgência daqueles que resultam de lesões do sistema nervoso central (CNS) e potencialmente em maior risco constitui um desafio. Como a análise isolada do tipo de nistagmo espontâneo não é suficiente para diferenciar os doentes com patologia periférica daqueles com patologia do sistema nervosa central, desenvolveram-se para este efeito algumas provas clínicas. Uma das mais importantes é o HIT. A ausência de sacada de refixação durante os impulsos ipsilesionais em doentes com nistagmo espontâneo e sem evidência de outros sinais e sintomas neurológicos, parece ser o que melhor prevê isoladamente a existência disfunção do CNS como causa do síndrome vestibular agudo⁴. A presença de nistagmo espontâneo constitui no entanto uma dificuldade adicional dado que as fases rápidas do nistagmo e a sacadas overt apresentam a mesma direção, ambas fazem o reset da fixação ocular e partilham propriedades cinemáticas. A realização de provas adicionais tais como o alinhamento ocular vertical (vertical skew) e sentido do nistagmo na leve e dextroversão aumentam o valor diagnóstico do HIT, mas requerem aptidões e competências habitualmente não disponíveis no serviço de urgência.

Dado que o vHIT permite a quantificação das respostas oculomotoras aos estímulos impulsivos e apresenta uma curva de aprendizagem rápida na execução da prova, procurámos realizar um conjunto de experiências com o objetivo de determinar se o envolvimento de vias vestibulares centrais causam alterações do VOR dinâmico objectiváveis com o vHIT. Colocámos como hipótese que tais alterações poderiam ser não só traduzidas num algoritmo para topodiagnóstico clínico mas também contribuir para a compreensão dos mecanismos neurofisiológicos de controlo do VOR impulsivo. Para tal estudámos indivíduos saudáveis, doentes com UVL e nistagmo espontâneo de origem periférica e central e doentes com diagnósticos específicos de doença neurodegenerativa hereditária, com e sem envolvimento das vias vestibulares centrais. Nos próximos parágrafos são sumariamente descritos os fundamentos, objectivos, métodos, resultados e conclusões das experiências realizadas.

⁴ Newman-Toker DE, Kattah JC, Alvernia JE, Wang DZ. Normal head impulse test differentiates acute cerebellar strokes from vestibular neuritis. *Neurology*. 2008;70(24 Pt 2):2378–85.

1. Experiências que avaliaram as respostas vestibulo-oculográficas com impulsos cefálicos numa população normal

O objectivo deste estudo foi estabelecer os valores normativos numa população normal. Foram avaliados 40 indivíduos, 55% mulheres e com idade 41.10 ± 16.6 , sem história conhecida de qualquer patologia do sistema nervoso central, do ouvido interno ou queixas de vertigem, tontura ou desequilíbrio. A latência média do VOR foi de -2.3 ± 2.1 , o ganho médio por regressão foi de 0.94 ± 0.08 e de 0.88 ± 0.09 aos 60 ms, com um valor médio de assimetria de 3.13 ± 2.00 . No respeitante às fases rápidas (QEM) não identificámos presença de sacadas covert e encontramos sacadas overt em 50% dos indivíduos, com uma taxa de ocorrência de 14.4 ± 20.1 , latência de 174.8 ± 52.4 ms e velocidade de pico de 82.5 ± 43.4 °/s. A taxa de ocorrência de sacadas anti-compensatórias foi de $0.3\% \pm 1.1\%$.

2. Experiências que avaliaram o valor topodiagnóstico do vHIT no Síndrome Vestibular agudo

Ganho da fase lenta e fases rápidas anticomensatórias

Durante a avaliação de doentes com UVL notámos a presença de QEM anticomensatórias (AQEM) em doentes com etiologia periférica de nistagmo espontâneo. No primeiro estudo apuramos o valor diagnóstico das AQEM e do ganho do VOR na discriminação dos doentes com etiologia periférica e central de Síndrome Vestibular Agudo. Todos os doentes com patologia periférica e todos os controlos positivos após neurectomia vestibular apresentaram AQEM durante os impulsos contralesionais. Os doentes com lesão vestibular central não apresentaram AQEM. A acuidade diagnóstica da taxa de ocorrência das AQEM foi de 100% (95% CI for AUC ROC curve: 1.0 to 1.0) enquanto a acuidade diagnóstica do ganho do VOR foi de 96% (95% CI for AUC ROC curve: 0.90 to 1.0). Estes resultados sugerem que as AQEM são um sinal de assimetria vestibular no contexto de um deficit periférico. Assim, a assimetria vestibular estática é repentinamente mas substancialmente aumentada durante o impulso cefálico contralesional, movimentando os olhos mais rapidamente em direcção ao lado lesado. Quando o olho alcança a posição excêntrica na órbita uma fase rápida do nistagmo espontâneo é desencadeada para reposicionar a fixação ocular. Estas fases rápidas são detectadas no vHIT como AQEM. Estes factos sugerem que os impulsos, tal como o piscar dos olhos, são reveladores de assimetrias vestibulares dinâmicas.

Na presença de um nistagmo espontâneo irritativo, situação em que o nistagmo apresenta a fase rápida com o mesmo sentido da lesão, estas fases rápidas anti-compensatórias não são observadas, pois durante os impulsos contralesionais ocorre, paradoxalmente, a diminuição da assimetria vestibular. Em resumo, as AQEM revelam assimetrias no tónus vestibular de origem periférica. Em doentes com nistagmo de origem vestibular central os impulsos cefálicos não desencadeiam AQEM.

Controlo dinâmico do ganho do VOR com impulsos cefálicos e origem canal dos potenciais evocados miogénicos

Aqui reportámos um doente com UVL e nistagmo espontâneo com origem numa Vertigem Posicional Paroxística Benigna (VPPB) e um plug espontâneo do canal semicircular horizontal. Tanto quanto sabemos demonstrámos pela primeira vez que a VPPB se pode apresentar com nistagmo espontâneo, e não somente com nistagmo pseudo-espontâneo. A avaliação deste caso peculiar com o vHIT revelou um perfil de saturação da velocidade do olho durante os impulsos ipsilesionais, acima de determinado valor de velocidade cefálica, resultante da modificação biomecânica do sistema cupulo-endolinfático pela presença de um *plug* ou *jammed* otoconial do canal semicircular horizontal. Para demonstrar a saturação da resposta ocular utilizámos um método de cálculo do ganho do VOR por regressão linear que viria a ser utilizado posteriormente em todas as investigações. Este perfil de saturação, bem como o nistagmo espontâneo normalizaram com manobras libertadoras, documentando também pela primeira vez uma deficiência da dinâmica de alta frequência do sistema cupulo-endolinfático. Também, tanto os potenciais evocados miogénicos vestibulares cervicais como os oculares se encontravam ausentes durante a estimulação ipsilesional, antes e após manobras libertadoras, recuperando entre os 30 e os 80 dias. Na ausência de sintomas de disfunção otolítica e excluída a lesão retrolabirintica, dada a resolução da sintomatologia com a manobra libertadora, concluímos tratar-se de lesão mecânica canal isolada. Mais ainda seria difícil justificar a recuperação de lesão sacular e utricular em menos de 80 dias. Esta argumentação desafia pois a origem única otolítica dos VEMP, sugerindo que também podem ter origem canal, tal como acontece nas deiscências do canal semicircular superior.

3. Valor topodiagnóstico do vHIT em lesões vestibulares não agudas

VOR impulsivo nos planos horizontal e verticais tem valor topodiagnóstico

Aqui reportámos um doente de 36 anos com oscilópsia, tontura e desequilíbrio progressivos, sem nistagmo espontâneo que apresenta na avaliação por vHIT 3D lesão selectiva do VOR no plano de ambos os canais semicirculares posteriores (0.49 ± 0.05 e 0.38 ± 0.06) e horizontais (0.38 ± 0.07 e 0.29 ± 0.05) com desencadeamento de sacadas covert e overt e preservação do VOR no plano de ambos os canais semicirculares anteriores (0.89 ± 0.08 e 1.04 ± 0.15). Dado que o nervo vestibular superior transporta aferentes primários dos canais semicirculares homolaterais anterior e horizontal e o nervo vestibular inferior aferentes primários do canal semicircular homolateral posterior, a combinação de lesão apresenta não é sugestiva de lesão no órgão periférico. A Ressonância magnética revelou a presença de uma lesão junto ao pedúnculo cerebeloso inferior sugestiva de um glioma. Dado que o flocculo inibe as respostas dos canais semicirculares superiores mas não as restantes e as fibras que lhe são dirigidas fazem um bypass ao núcleo vestibular e são conduzidas através do pedúnculo cerebeloso inferior, especulámos que poderia ser a redução desse efeito inibitório que poderia justificar o maior ganho no plano de ambos os canais superiores. Tanto quanto sabemos, este terá sido o primeiro caso reportado do valor topográfico da avaliação da resposta dos 3 pares de canais semicirculares.

4. Experiências que avaliaram o valor topodiagnóstico do vHIT em doenças neurodegenerativas hereditárias

Respostas do VOR dinâmico durante impulsos cefálicos na doença de Huntington, sem envolvimento das vias vestibulares

Aqui estudámos doentes com diagnóstico geneticamente confirmado de doença de Huntington ($n=18$; 44.7 ± 8.1 anos; 9 mulheres) . Com este estudo pretendemos estudar doentes com ataxia cerebelosa hereditária sem envolvimento conhecido do sistema vestibular. Dado que os estudos disponíveis avaliaram unicamente as baixas frequências do VOR, com estimulação calórica e cadeira rotatória, pretendemos em primeiro lugar verificar que o não envolvimento do sistema vestibular se estendia às altas frequências do VOR testadas com os impulsos cefálicos. Os valores de latência

do VOR e do ganho de VOR não foram diferentes dos do grupo controlo (n=40; $p>0.29$ para ambas as comparações), nem se verificou diferença entre os doentes pré-sintomáticos e sintomáticos. Os QEM foram unicamente do tipo overt e compensatórios, com taxa de ocorrência (0.45 ± 0.29), velocidade de pico ($71.58\pm 34.48^\circ/\text{s}$) e latência (174.5 ± 41.2 ms) que não foram diferentes das do grupo controlo ($p>0.11$ para todas as comparações). De forma não voluntária e não consciente, 5 dos doentes sintomáticos não conseguiram gerar movimentos descentrados dos olhos, tanto vertical como horizontalmente, tal correlacionando-se com o *Total Functional Capacity* (TFC) scores (Spearman $r=0.65$, $p=0.005$). O VOR parece assim estar preservado na doença de Huntington nas frequências fisiológicas, mesmo nas fases mais avançadas da doença. Muito embora seja conhecido que tanto as sacadas voluntárias como as fases rápidas do nistagmo são mais lentas na doença de Huntington, as fases rápidas durante os testes de impulse cefálico não mostraram diferença em comparação com os controlos.

Respostas do VOR dinâmico durante impulsos cefálicos em ataxias hereditárias, com envolvimento das vias vestibulares

Neste estudo avaliámos doentes com diagnóstico geneticamente confirmado de ataxia espinocerebelosa (SCA) tipo 3, tipo 1 e tipo 2 e ataxia de Friedreich (FA), procurando alterações das vias vestibulares centrais. Os resultados de ganho e VOR revelaram um aumento da latência em FA ($p<0.001$) e SCA3 ($p=0.02$) em comparação com os controlos e discriminando FA dos outros doentes atáxicos com uma acuidade diagnóstica de 88%. Os ganhos por regressão e instantâneos a 40 e 60 ms foram também significativamente mais baixos em SCA3 e FA ($p<0.001$), mas unicamente em SCA3 aos 80 ms, discriminando estes dos restantes doentes atáxicos com uma acuidade diagnóstica de 78%. O ganho de VOR por regressão mostrou ainda uma correlação negativa com a severidade por avaliada pela Scale for the Assessment and Rating of Ataxia (SARA) (Spearman $r=-0.46$, $p=0.01$). As sacadas covert foram unicamente desencadeadas em SCA3 mas com baixa taxa de ocorrência e velocidade de pico ($11.1\pm 28.5\%$ and $77.50\pm 15.30^\circ/\text{s}$) enquanto as sacadas overt foram desencadeadas em todos os grupos. O controlo dinâmico de VOR encontra-se assim comprometido em SCA3 mas não em FA. O VOR impulsivo parece ser controlado por feedback interno, baseado na previsão do erro de fixação, e atualizado com estratégias pré-programadas, ajustando *online* a velocidade da fase lenta, o que ocorre aos 80 ms em FA mas não em SCA3, ou desencadeando sacadas covert, o que ocorre

em SCA3 mas não em FA. Concluimos que o vHIT fornece informação fenotípica que diferencia as ataxias autossómicas mais comuns, que podem nomeadamente ser utilizadas como estratégia para a orientação do diagnóstico genético. Por outro lado a presença de sacadas overt, tal como anteriormente demonstrado nas ataxias não hereditárias, poderá promover a identificação de falsos positivos, pois presentes em todos os grupos, nomeadamente no grupo controlo. Por fim, a correlação entre o VOR e SARA levanta a possibilidade de utilização do VOR como biomarcador neurofisiológico da severidade da doença.

Conclusões

Globalmente o resultado destes seis estudos fornece dados relevantes na avaliação de transtornos vestibulares centrais e periféricos, nomeadamente na vertigem aguda onde rápido topodiagnóstico poderá ser mais importante. Primeiramente demonstrámos que não só o estudo do ganho instantâneo da fase lenta tem valor topodiagnóstico mas também a análise da variação dinâmica do ganho, como no caso do plug do canal semicircular horizontal ou em SCA3. Também a combinação selectiva dos canais semicirculares afectados apresenta valor topográfico como mostrámos no paciente com o glioma do pedúnculo cerebeloso inferior. Em segundo lugar demonstrámos que a análise das fases rápidas (QEM) apresentam igualmente valor topodiagnóstico. Muito embora tenha ocorrido grande resistência da comunidade científica a este conceito é hoje reconhecido que também as fases rápidas deverão ver analisadas a sua latência, velocidade de pico, direcção e taxa de ocorrência na interpretação do vHIT.

Por fim as respostas oculomotoras geradas pelos impulsos cefálicos forneceram dados neurofisiológicos para a compreensão tanto do biomecanismo cupulo-endolinfático e dos processos de controlo dinâmico do VOR como da neuromodulação do nistagmo espontâneo vestibular durante os impulsos cefálicos.

Em conclusão, o vídeo Head-impulse Test permite a quantificação das repostas oculares após impulsos cefálicos, sendo uma medida objectiva da resposta oculomotora a estímulos fisiológicos, isto é, sinais de aceleração e de velocidade apresentados nos planos dos canais semicirculares. É particularmente útil na avaliação de cabeceira em doentes vestibulares agudos e

com nistagmo espontâneo mas também no *follow up* regular, fornecendo informação relativamente à lateralidade, grau de disfunção, presença de nistagmo espontâneo vestibular e topodiagnóstico. Deste modo, permite a adequação da terapêutica farmacológica e reabilitação vestibular, a obtenção do valor prognóstico e a documentação da recuperação completa ou sequelar do episódio agudo. Uma vez que permite a análise, reanálise e partilha de dados será de esperar uma rápida e massiva disponibilização de informação e conhecimento. Esta, deverá conduzir a uma melhor caracterização fenotípica e topográfica das diferentes entidades patológicas e sindrômicas. É, por fim, uma oportunidade única para o estudo da fisiopatologia da aprendizagem, retenção e controlo do reflexo vestibulo-oculomotor após lesão vestibular, conhecimento este essencial para o desenvolvimento de novas e mais eficazes estratégias de reabilitação e reeducação vestibular.

CHAPTER I

GENERAL INTRODUCTION AND LITERATURE REVIEW

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I. The Human Vestibulo-Ocular Reflex (VOR) with Head Impulses

Dizziness and vertigo are highly prevalent symptoms (Brandt et al. 2010) that accompany a variety of conditions. Central lesions causing dizziness and vertigo can usually be identified by MR brain imaging (multiple sclerosis, brain tumours or strokes). The majority of dizzy patients, however, suffer from vestibular and non-vestibular disorders, often without an observable neuroanatomical correlate. Since the treatment for all of these conditions should be directed towards the underlying disease, the clinician must be able to test the vestibular function in order to understand and quantify the integrity of the peripheral and central vestibular circuitry. Currently, this assessment, both at the clinical and laboratory level, is achieved primarily through semicircular canal (SCC) stimulation with eye movement analysis.

Horizontal rotations of the head generate compensatory conjugate eye movements, of equal magnitude and opposite direction, known as the vestibulo-ocular reflex (VOR) (Lorente de Nó 1933). The main objective of this reflex is to stabilize visual input during head motion. Hair bundles in the ampullary *cupulae* of the semicircular canals (SCC), aligned with the endolymph movement, transduce mechanical forces into electrochemical signals, increasing the vestibular nerve tonic firing rate ipsilaterally and decreasing it contralaterally (Goldberg and Fernández 1971), ultimately stabilizing gaze via the brainstem neural circuitry (Kennard and R John Leigh 2011). If the angular acceleration is maintained, the VOR slow phase is interrupted by a quick phase with kinematical similarities to a refixating saccade (Ron et al. 1972; Curthoys 2002) and in the same direction as head rotation, thereby resetting gaze. These quick phases are clinically recognized as nystagmus fast phases and as spontaneous nystagmus in case of a static vestibular asymmetry.

The Head Impulse Test (HIT) (Halmagyi et al. 1988, 1990b) is a clinical test of vestibular function in which a VOR slow phase is generated. This maneuver tests the angular VOR by applying low amplitude (10-25°), high-acceleration (3.000-6.000°/s²) and velocity (150-300°/s) head rotations, along the horizontal or vertical coplanar SCC pairs, while instructing the patient to maintain visual fixation straight ahead at a particular point, e.g., the examiner's nose. The stimulation has to be fast enough in order to drive the contralateral coplanar SCC afferents into inhibitory saturation (Ewald 1892; Halmagyi et al.

1990a, 2001), and therefore unilaterally stimulate only one of the coplanar SCCs. If the ipsiversive VOR slow-phase is intact, the patient will be able to maintain visual fixation on the target throughout the impulse (**Figure 1A and supplementary video 1**). In contrast, if the VOR slow phase is non-compensatory, the gaze will be off-target after the movement and the patient will re-fixate the target with a saccade (**Figure 1B and supplementary video 2a**). As the VOR slow phase cannot be clinically evaluated, the identification of this re-fixating saccade is interpreted as an indirect sign of vestibular deficit and the HIT, therefore, is considered pathologic toward the side being tested. Although the HIT is a clinical test of unquestionable utility, it has shown to have a relatively low sensitivity (63%) and specificity (78%) in detecting unilateral vestibular lesions (UVL), as identified with scleral search coils, even when performed by experienced clinicians, (Jorns-Haderli et al. 2007). Paradoxically, non-experts have reached better sensitivity scores, as experts might tend to accept borderline results as normal.

Figure 1. Head Impulse Test.

A



B



A) Normal response. With a quick head movement to the right, the patient is able to keep the eyes on the target (in this case, the patient is looking at the camera). B) Right pathologic Head Impulse Test. With a quick head movement to the right, the patient is unable to keep the eyes on the target; the eyes follow the head and a catch-up saccade is triggered to re-fixate the target.

HIT *quantification* with scleral search-coil recording (Aw et al. 1996a; 1996b; Schmid-Priscoveanu et al. 2001) and, more recently, electro-oculography (Hirvonen et al. 2007; Jutila et al. 2012; 2013) and video-oculography recording [video HIT (vHIT)] (Lehnen et al. 2008, Bartl et al. 2009; MacDougall et al. 2009), overcomes most of the clinical HIT limitations. While the clinical HIT only allows the identification of saccades triggered after the head impulse, the quantification of the HIT further allows the identification and characterization of both the VOR slow-phase and quick eye movements. The former is generated during the head movement and the latter are generated both during and/or after the head impulse. They are referred to as covert and overt saccades, respectively (Weber et al. 2008a). While the overt saccades can be observed clinically, the covert saccades typically are not identified. Furthermore, since overt and covert saccades have the direction of the VOR slow phase, they are considered catch-up saccades, in analogy to smooth pursuit catch-up saccades (Tian et al. 2000).

II. Literature review

Methods

Published studies were identified through a literature search using MEDLINE (PubMed), Google Scholar and extensive searching using cross-references from original articles and reviews through June 2014. The search strategy for electronic database searches was performed by combining the terms video OR oculography OR video-oculography OR videonystagmography OR camera OR "video recording" with the terms vestibulo-ocular reflex OR head impulse test OR head thrust. All terms were searched as indexed [MeSH] and as free text terms to increase recall. Language was restricted to English and the search was limited to studies conducted in humans. Titles, keywords and abstracts of the citations downloaded from the electronic search were screened and full copies of reports were obtained when judged suitable for further assessment. Studies were considered eligible for inclusion in this review if the authors used the vHIT to evaluate clinical physiological parameters in control subjects or actual patients. We excluded studies dealing exclusively with search coils and studies using devices not yet compared with coils. Two authors (L.L. and J.C.) independently assessed the reports identified by the search strategy. Details about the characteristics and results of the studies were obtained independently

and crosschecked for accuracy. Consensus was used to resolve any disagreement, and a descriptive analysis was performed. Following these eligibility criteria, and after de-duplication of search results, we were able to include for purposes of analysis 41 published studies.

1. vHIT (video Head Impulse Test) recording

1.1 Recording systems.

Table 1 shows the summary of the revised studies on vHIT recording systems.

While coils are still the gold standard for HIT quantification, they present several technical issues that render them difficult to use outside of the research laboratory. In contrast, vHIT recording is non-invasive, significantly easier to use in the clinical setting, such as in the emergency department or outpatient clinic, and it is considerably less expensive. The weight, size, spatial resolution and sampling rate of new digital cameras allow HIT quantification with significant concordance correlation with coils (Bartl et al. 2009; MacDougall et al. 2009; Weber et al. 2009; Lehnen et al. 2010; Agrawal et al. 2014; MacDougall et al. 2013). Together with a gyroscope that measures head velocity and firmly tight goggles, they are used to capture and record eye and head movements (**Figure 2a**). Another type of video recording system is also available, which is not head-mounted, but mounted on a remote tripod (Ulmer and Chays 2005; Ulmer et al. 2011; Murnane et al. 2014). However, since we could not locate any study comparing this system to the gold-standard search coils, they were not included in this review.

First, the horizontal and vertical eye position must be calibrated by having the patient fixate luminous dots either projected by a head-fixed laser or displayed on a screen at predefined horizontal and vertical angles (**Figure 2c**). VOR then is obtained by manually delivering at least six valid (Glasauer et al. 2004) high velocity (200-300°/s) and low amplitude (10-20°) head impulses in each SCC coplanar direction. (**Figure 2b**) The available systems usually automatically reject the head impulses that do not meet these criteria. The push-pull planes are the horizontal plane, along the horizontal SCC and two (diagonal) vertical planes: LARP (along the left anterior and right posterior SCC), and RALP (along the right anterior and left posterior SCC). In each push-pull plane, impulses should be unpredictable in both time and direction, while patients are

asked to fixate a target (usually a printed dot on a white board) at more than 140 cm distance, on the midline and at eye level (**Fig. 2b**).

Figure 2. vHIT system example.



A) vHIT goggles, a camera with integrated accelerometer and a laser for calibration. (EyeSeeCam, EyeSeeTec GmbH, Munich, Germany). B) vHIT *setup*. The system is first calibrated by having the patient fixate luminous dots projected by the head-fixed laser. After calibration, horizontal recordings (h-vHIT) are obtained by manually delivering at least 6 valid high velocity ($150\text{-}300^\circ/\text{s}$) and low amplitude ($10\text{-}20^\circ$) head impulses in the direction of both horizontal SCC, to each side, both time and direction unpredictable, while patients are asked to fixate a printed dot on a white board at 140 cm distance on the midline and at eye level. Vertical recordings (LARP, left anterior-right posterior; RALP, right anterior-left posterior) are obtained along vertical canal planes.

Table 1. Summary of the revised studies on vHIT recording systems

Authors	Device	Study type	Population size	Disease	Main Finding
Bartl et al., 2009	Head mounted	Pivotal/ Prospective and comparative (vs. search coils)	Controls (n=1)	NA	vHIT enables hVOR quantification; goggle slippage is a technical issue
Weber et al., 2009	Head mounted	Pivotal/ Prospective comparative (vs. search coils) and controlled	Patients (n=2), Controls (n=1)	VN, vestibular schwannoma	vHIT enables hVOR quantification and detects covert and overt saccades
Colagiorgio et al., 2013	Head mounted	Prospective and controlled	Patient (n=2) Control (n=1)	VN	The combined measurement of eye and head movements together with the timing of an optotype on screen that needs subject identification allows functional VOR testing

hVOR: VOR gain in the plane of the horizontal semicircular canal; NA – not applicable; vHIT: video Head Impulse Test; VN: vestibular neuritis; VOR: vestibulo-ocular reflex.

2. Evaluation parameters.

The vHIT permits the evaluation of the VOR slow phase and the characterization of the quick eye movements triggered both during, as well as after, the head impulses. Normative data for VOR slow-phase gain and physiological catch-up saccades are shown in **Table 2**.

2.1. VOR slow phase.

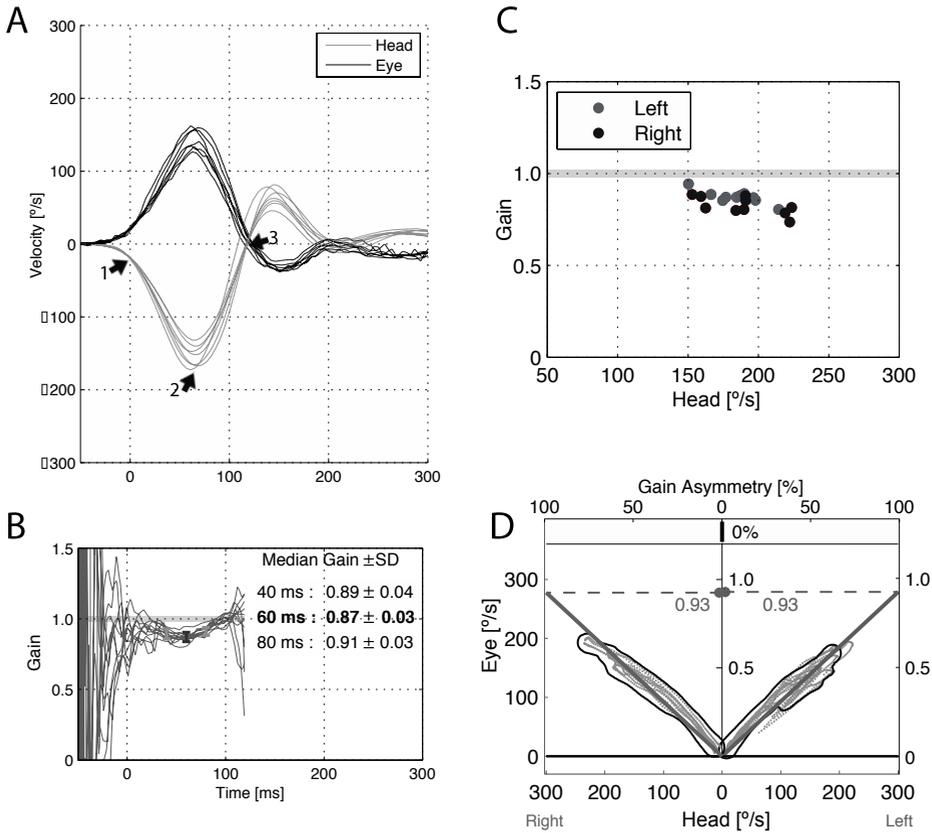
Three instances during an impulse should be defined in advance: the head impulse start, which, for example, can be defined as the time when head velocity exceeds $20^\circ/\text{s}$ (Glasauer et al. 2004), the head peak velocity or peak acceleration, where velocity or acceleration reach their maximal values, and the head impulse end, when head velocity crosses $0^\circ/\text{s}$ and typically rebounds (Weber et al. 2008) (**Figure 3a**).

The recording of eye and head movements during the impulse allows for the estimation of both the *VOR latency*, calculated as the eye velocity minimum lag time with respect to head velocity from $20^\circ/\text{s}$ to $70^\circ/\text{s}$ (Aw et al. 1996b), as well as the *VOR gain*, calculated as the ratio between these velocities. Healthy subjects exhibit short latency compensatory vestibular VOR slow phases (Aw et al. 1996b; Collewijn and Smeets 2000), which means that eye velocity mirrors head velocity and that VOR gain is close to unity. In contrast, UVL patients show prolonged latency and deficient VOR slow phases during ipsilesional impulses. They also trigger saccades during and/or after the head impulse (Aw et al. 1996a; Tian et al. 2000; Weber et al. 2008). In spite of the attention that vHIT has raised, latency only recently has been addressed with the vHIT in hereditary ataxias (Luis et al. 2014a). In contrast, gain is the central variable for estimating VOR function, and there are several algorithms to calculate gain.

With coils, VOR gain is calculated as an instantaneous function (*instantaneous or velocity gain*) (Aw et al. 1996b; Collewijn and Smeets 2000; Lehnen et al. 2004), so that data can be read at a given time, for example at 40 ms (Glasauer et al. 2004) (**Figure 3b**). If gain is calculated according to head speed, it is known as *speed gain* (**Figure 3c**). Gain also can be calculated as a linear regression for a period after head impulse start (Lehnen et al. 2004) or prior to peak head velocity or acceleration (Aw et al. 1996b; Collewijn and Smeets 2000; Lehnen

et al. 2004) (*regression or acceleration gain*) (**Figure 3d**). More recently, VOR gain has been calculated with the vHIT as a function of the area under the desaccaded eye velocity and the head velocity curve (*area or position gain*) (MacDougall et al. 2013).

Figure 3. Normal vHIT along the plane of the horizontal SCC – Illustratory example.



A) Velocity profile plot. In each trial and for all valid head impulses, this plot shows the velocity trajectories (°/s) of the eye (black) and head (grey) during right impulses. 1 is the head impulse start, 2 the head velocity peak and 3 the head impulse end. B) VOR instantaneous gain plot shows the time course (ms) of the VOR gain (eye velocity/head velocity); instantaneous median gain and standard deviation are calculated at 40, 60 and 80 ms. C) Head velocity instantaneous gain plot shows VOR gain values at 60 ms as a function of peak head velocity for right and left impulses. D) Velocity regression plot shows the regressions of eye and head velocity during right and left impulses.

The instantaneous VOR gain at 40 ms after head impulse start (Glasauer et al. 2004), 30 ms to peak velocity (Agrawal et al. 2014) or a 40 ms regression gain

starting at 50 ms after head impulse start (Lehnen et al. 2004) among others, all have been used as common parameters determined with the use of coils to estimate VOR gain. These parameters naturally have been transferred to the first vHIT gain calculations (Lehnen et al. 2008; Bartl et al. 2009; Weber et al. 2009). The justification is that during these early time points, the short-latency VOR is the only system that contributes to eye velocity and that contaminations from other longer-latency ocular motor systems, such as catch-up saccades, do not yet occur (Aw et al. 1996).

The recently introduced *position gain* may show some disadvantages. Although recognized bump artefacts (**Figure 6**) and their partial cancellation of phases might have justified this new calculation approach (MacDougall et al. 2013b), it takes into account the velocity ratio during the whole impulse, from head impulse start (defined as 60 ms before head peak velocity) to head impulse end, which typically occurs long after 100ms. After such a long time, however, covert saccades already might be triggered, among other contaminations from the ocular motor system (smooth pursuit, optokinetic system, ocular following, and cervico-ocular reflex). This method, therefore, needs desaccadation. Quick eye movements occurring during the impulses have to be identified and removed, in order to avoid a false VOR gain increase (MacDougall et al. 2013a; MacDougall et al. 2013b). Although this method has shown comparable results with coils when using the same new calculation method, i.e., position gain, it still has not shown comparable results with the “traditional” calculation methods, which are instantaneous and regression gains. Such a circular comparison of a new method with itself can miss contaminations that affect both devices; for example, the effects from other ocular motor systems. In addition, position gain also might be contaminated by false saccade detection. In Figure 4 by MacDougall et al. (2013b), for example, “bump” artefacts are mistaken for saccades and marked with red colour by the desaccadation algorithm. This also means that bump artefacts can be considerable, even fulfilling the criteria for saccades. Finally, this method implicitly discards the effect of latency on the gain value, as an increased latency (or a slippage effect) should lead to a reduction of gain (Palla and Straumann 2004).

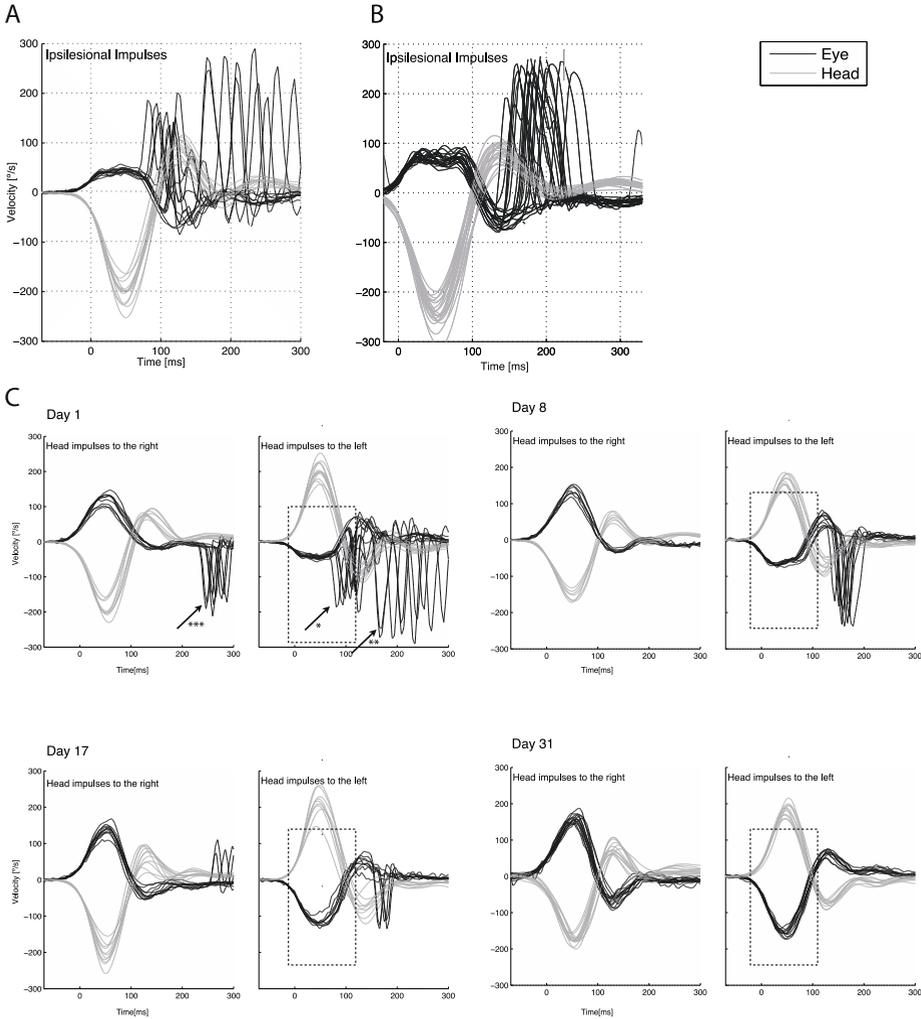
A VOR gain greater than unity has been reported for presbyopic older individuals (Agrawal et al. 2014) and it likely results from the use of magnifying spectacles, as these have been shown to temporarily increase gain (Crane and Demer 2000). Also, it may result from goggle slippage, namely, depending on how well the goggles fit the nose and the orbital region of the subject (Versino

et al. 2014). In contrast, gain decrease is the main characteristic in diagnosing an abnormal canal function with the vHIT. Low gain cut-offs (2 standard deviations below mean) of 0.75 for instantaneous gain at 60 ms (Mossman et al., 2014), 0.79 for instantaneous gain at 80 ms (Mossman et al., 2012), and 0.79 for 40-80 ms averaging (Blödown et al. 2013), 0.78 for regression gain (Luis et al. 2014a) and 0.80 for position gain (Pérez-Garrigues et al. 2014) suggest that close results may be obtained with these calculation methods in normal subjects. Still, this does not validate the ability of these algorithms to detect pathologic VOR responses in patients.

Evaluating the dynamic gain changes during the impulse allows the identification of different characteristic velocity profiles, e.g., a vestibular neuritis (**Figure 4a**), and a SCC plug profile (**Figure 4b**) (Luis et al. 2013). In the latter, the eye velocity saturates and remains constant above a certain head velocity, thus suggesting a cupular biomechanical change.

Contralesional gain also may show low values. During contralesional impulses (towards the healthy side), UVL patients may generate deficient VOR slow-phases. Although, in such cases, the contralesional VOR excitatory pathway is preserved, the gain reduction likely results from the defective ipsilesional VOR inhibitory pathway (Aw et al. 1996a; Palla and Straumann 2004). The same push-pull total sum mechanism explains why patients with unilateral vestibular lesion may show relatively normal slow phases during low velocity ipsilesional head rotations, as the healthy contralesional side compensates for the loss. According to Ewald's 2nd law (Ewald 1892; Halmagyi et al 1990; Weber et al. 2008a,b) the contralesional vestibular signal saturates at higher velocities and the VOR defect is unmasked, justifying why impulses must be fast (Machner et al. 2014).

VOR gain asymmetry can also be determined with vHIT using an analogous Jongkees formula (Jongkees et al. 1962) for canal paresis in caloric testing [(higher gain -lower gain) / (higher gain + lower gain)]. In the first author's lab data, the VOR asymmetry presents significantly lower cut-off values than calorics (7.0% vs. 25.0%) and it is used in addition to VOR gain cut-offs in search for normality.

Figure 4. Acute vestibular lesion illustrative examples.

A) Vestibular neuritis. During ipsilesional impulses, the eye velocity curve is a non-compensatory trajectory, and refixating saccades are triggered. B) Horizontal semicircular canal plug. During ipsilesional impulses the eye velocity curve is non-compensatory but presents a saturated profile; refixating saccades are triggered. C) Left vestibular neuritis recovery. The right beating spontaneous nystagmus reaches 7.60 angular slow-phase velocity (aSPV). Note the defective slow phase during left impulses (instantaneous gain is 0.17, 0.18 and 0.25 at 40, 60 and 80 ms, respectively); regression gain is 0.25 to the left and 0.69 to the right (inferior to the normal lower limit 0.78, calculated as average-2SD), the asymmetry between sides reaching 46%..

Covert (* arrow) and overt (** arrow) saccades are triggered during left impulses. During every right head impulse $200^\circ/\text{s}$ anti-compensatory quick-eye movements (***) arrow; AQEM) are triggered at about 240 ms, increasing the visual error generated by a defective VOR slow phase. Day 8: There is no spontaneous nystagmus. During ipsilesional impulses, the slow phase gain increased to 0.48 at 60 ms and no covert saccades are triggered. During contralesional impulses AQEM are no longer triggered. Day 17: the slow phase gain at 60 ms increased to 0.60 and 0.70 during left and right impulses, respectively. Overt catch-up saccades are triggered bilaterally. Day 31: The slow phase gain is now compensatory (0.92 and 0.90 at 60 ms). There are no catch-up saccades triggered with the head impulses.

2.2. Quick eye movements (QEM) with head impulses

Quick eye movements are identified as bidirectional peaks and are classified according to their latency after head impulse start (ms), peak velocity ($^\circ/\text{s}$), and occurrence rate (the percentage of impulses with QEM). QEM further can be quantified according to the amplitude of the generated eye movement ($^\circ$). These eye movements may present the same direction of a non-compensatory VOR slow phase and, therefore, contribute to decreasing the gaze position error. In analogy to the fast phases of saccadic pursuit, these QEM are known as **catch-up or refixating saccades**. In cerebellar lesion patients, for example, VOR gain can be higher than unity (Choi et al. 2013). In such cases QEM will present the opposite direction of the VOR slow-phase; nevertheless, they still will be considered compensatory saccades because they bring the eye back to the target. In contrast, *anti-compensatory* QEM move the eyes away from the target (Heuberger et al. 2014; Luis et al. 2014c).

Saccades that are triggered with head impulses, either compensatory or non-compensatory, are qualitatively classified as **covert** (Weber et al. 2008), if generated during the head impulse, and **overt**, if generated after the head impulse (**Figure 4c**). Given their short latency, before the end of the rapid head movement impulse, covert saccades cannot be visualized clinically (**Figure 5a**), but may compensate VOR so effectively that no overt saccades are triggered, as gaze remains on target after the head impulse (**Figure 5b and supplementary video 2b**). In healthy controls, overt saccades with particularly low peak velocity and low occurrence rate may be physiological (**Table 2**). In contrast, covert saccades are characteristic of a vestibular lesion. Overt saccades seem to result from a gaze position error and, therefore, need a target

to be initiated. Preliminary studies in bilateral vestibular lesion (BVL) patients suggest that catch-up saccades after passive head impulses require visual input, as in darkness they are possible only with residual vestibular function (Lehnen et al. 2013).

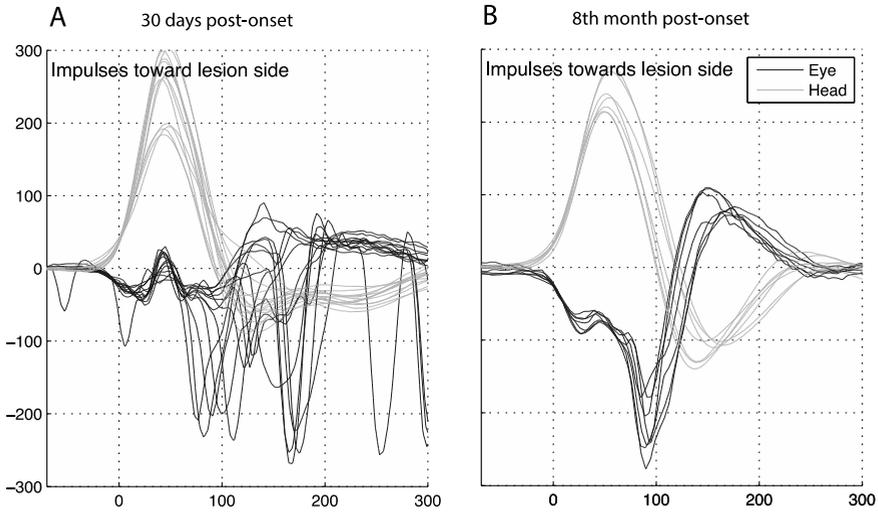
Nystagmus fast phases also may be visualized in vHIT recordings. Differentiating fast phases from catch-up saccades may be difficult simply by looking at vHIT plots (**Figure 4a**). Vestibular parietic nystagmus can be particularly noticeable during contralesional impulses as overt AQEM (Luis et al. 2014c), i.e., overt saccades with the opposite direction of the VOR slow phase (**Figure 4c**). AQEM presence suggests that spontaneous nystagmus is modulated by impulses and, therefore, should be of peripheral origin.

Covert AQEM followed by compensatory overt saccades have also been described in older individuals. In contrast to overt AQEM in acute vestibular syndrome (AVS) (Hotson and Baloh 1998), these seem to result from rather small static and dynamic VOR asymmetries caused by a vestibular deficit on the contralateral side and, therefore, also should be of peripheral origin (Heuberger et al. 2014). In this respect, they may help differentiate vestibular migraine from Ménière's disease.

2.3. VOR Functional Testing

Functional testing of the angular VOR has been an alternative diagnostic tool for identifying VOR deficits during passive head mobilization without measuring the eye and head movements (Longridge et al., 1987). Recently, an adaptation of the vHIT has been proposed where an optotype is briefly displayed on a computer monitor during the head impulse, testing the ability of the subject to read it. This then introduces a functional perspective to the vHIT, based on a successful reading and error trial (Colagiorgio et al. 2013).

Figure 5 vHIT recording of a patient with acute and chronic UVL



A) 30 days post-onset. During ipsilesional impulses (left) the VOR slow phase is non-compensatory and covert and overt refixating saccades are triggered (Supplementary video 2a). B) 8th month post-onset. During ipsilesional impulses, the VOR slow phase is non-compensatory (VOR gain at 60 ms is 0.37); systematic covert saccades are locked at 60 ms. These catch-up saccades substitute for VOR so effectively that no overt saccades are triggered, meaning that the gaze remains on target after the head impulses. The clinical HIT in this patient is bilaterally normal (Supplementary video 2b)

3. vHIT comparative studies.

In this section, we review the studies that provided data for comparing vHIT recordings with other neurophysiological and clinical assessment tools of the vestibular function. **Table 3** summarizes these vHIT comparative studies.

3.1. vHIT vs. scleral search coils.

With the advantages of being non-invasive and easier to use in the clinical setting, vHIT instantaneous gain results were shown to be strictly correlated and closely comparable to the gold standard scleral search coils, in normal subjects as well as in UVL and BVL patients (MacDougall et al. 2009; Agrawal et al. 2014). This suggests that vHIT can be routinely used for quantitative VOR estimation and quick eye movement characterization at a clinical level and in larger scale cohort studies. However, more recent studies evaluating both the horizontal and vertical canals (MacDougall et al. 2013a; MacDougall et al. 2013b) have revealed differences between instantaneous vHIT and coil gains.

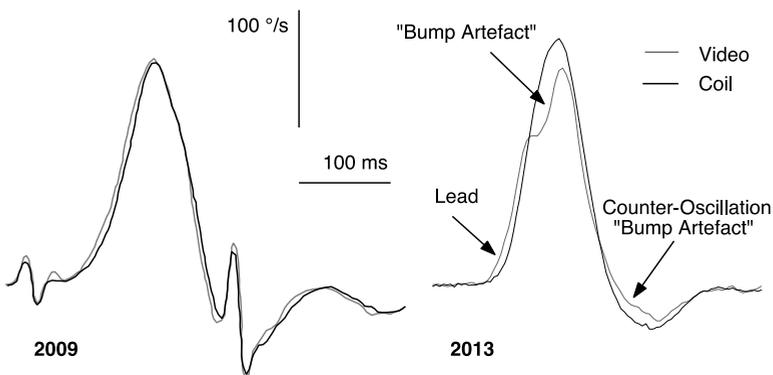


Figure 6. Direct qualitative comparison of video (black) and search coil (gray) eye velocity recordings. The traces are extracted from Figure 2E of MacDougall et al (2009) (left) and from Figure 2 L Lateral of MacDougall et al (2013) (right). Although the same device has been used in both recordings, the 2009 video trace shows good concordance with coil, which, however, was not reproduced by the later recordings from 2013. The latter shows marked “bump artefacts”, one during acceleration and another one during the slower counter-oscillation. Note that the “Counter-Oscillation Bump” occurs outside the range of AUC gain calculation after eye velocity has crossed the zero line.

Table 2. vHIT normality data

Authors	Population size	hVOR; cutoff						Saccades		
		VOR ₄₀	VOR ₆₀	VOR ₈₀	VOR _r	VOR _p	Asymmetry (ms)	latency	peak-velocity	occurrence
MacDougall et al. 2009	n=8	-	-	-	NA; 0.68*	-	-	-	-	-
Mossman et al., 2012	n=60	-	0.94±0.10; 0.75	0.97±0.09; 0.79	-	-	-	-	-	-
Blödown et al., 2012	n=20	-	0.96 ± 0.08**; 0.79	-	-	-	-	215±19	60±19	-
Pérez-Garrigues et al., 2014	n=10	-	-	-	-	0.99/ 1.01 (L/R); 0.8	-	-	-	-
Versino et al., 2014	n=13	-	0.98±0.06/1.03±0.06***; -	-	-	-	-	-	-	-
Candidate's own data (unpublished)	n=40	-	-	-	0.94±0.08; 0.78	-	3.13±2.00; 7.13	174.8±52.4	82.5±43.4	14.4±20.1

hVOR: VOR gain in the plane of the horizontal SCC; NA: not available; VOR₄₀: VOR instantaneous gain at 40 ms; VOR₆₀: VOR instantaneous gain at 60 ms; VOR₈₀: VOR instantaneous gain at 80 ms; VOR_r: VOR linear regression gain; VOR_p: VOR position gain

* Linear regression gain was calculated as ratio of mean eye velocity over mean head velocity during a 40-msec window centered at peak head acceleration

** (VOR₄₀, VOR₆₀, VOR₈₀) averaging

*** Ratio of the mean eye velocity over the mean head velocity computed over the time interval between head peak acceleration and peak velocity for right and left impulses

Initially, simultaneous search coil and vHIT recordings showed good correlation (**Figure 6**), and individual traces from the two methods were closely superimposed (MacDougall et al. 2009). These results appeared to justify the use of lightweight goggles (Weber et al. 2009) as a solution to overcome the slippage observed previously in another head-mounted video device (Lehnen et al. 2008; Bartl et al. 2009). Later, however, the close superposition of search coil and vHIT traces (MacDougall et al. 2009, Figure 2) could not be reproduced in a study using the same lightweight goggles (MacDougall et al. 2013a, MacDougall et al. 2013b). Instead, artefacts were reported which “are located just at the spot where VOR gain has traditionally been measured” (Figure 6) thereby causing considerable differences between coil (up to 0.46) and video (up to 0.92) gain (MacDougall et al. 2013, Figure 8).

In the meantime, other studies that relied on the good correlation between the two methods reported earlier (MacDougall et al. 2009), indeed, might have based their conclusions on false-negative vHIT outcomes, either by stimulating too slowly in order to avoid the artefacts (Manzari et al. 2012b, Figure 1), or by not taking the possible vHIT bump or slippage artefacts and their higher gains into account (Manzari et al 2012a, Figure 2). Another study comparing clinical HIT with vHIT (Pérez-Fernández et al 2012) reported, for example, normal vHIT gains together with refixation saccades. These observations, however, might once again be attributed to non-impulsive head stimulations and bump-induced gain increases. What is considered a “normal vVOR” (Pérez-Fernández et al 2012, Figure 1), shows, in fact, increased gains to the right at head velocities below 150 °/s and an above-normal asymmetry of 8.4%. What the purely gain-based vHIT analysis considers as “normal gain and saccades” (Pérez-Fernández et al 2012, Figure 3, Class 4), is, in fact, a clearly abnormal finding, even at head stimulation velocities below 150 °/s. The authors apparently assumed that the vHIT “velocity profile recorded was identical” with the coil, as suggested by MacDougall et al (2009, Figure 2 D and E), and that the validation against the coil “has shown an almost complete correspondence of results.” However, such identical velocity profiles subsequently could not be reproduced any more in a direct comparison of the methods (MacDougall et al 2013b, Figures 2 and 4).

An attempt to solve the problem of “bump” artefacts was to abandon the “traditional” instantaneous gain calculation method in favour of an *area under the curve* or *position gain* calculation, which essentially is the same as averaging the gain over a longer period of time, exceeding the limit of 100 ms (MacDougall

et al. 2013a; MacDougall et al. 2013b). Only with this new method was a good correlation with search coil data obtained. Why the “traditional” vHIT gains correlated so well with the search coil gains earlier (MacDougall et al. 2009), but not in the more recent study using the same device (MacDougall et al. 2013b), remains unexplained.

3.2. vHIT vs. clinical HIT.

In vertigo and dizziness outpatient cohorts, HIT identification of pathologic vHIT has reached relatively high sensitivity (0.93) but lower specificity (0.72) in acute disease diagnosis and vice versa in non-acute disease diagnosis (0.59 and 0.93, respectively) (Mahringer and Rambold 2014), in agreement with previous coil quantification data (Jorns-Haderli et al. 2007). "Relatively lower diagnostic accuracy in identifying pathologic vHIT has also been reported (Perez-Fernandez et al. 2012), as in that study nearly two-thirds of patients with normal VOR gain along the horizontal semicircular canal plane (hVOR), but with overt saccades of slow velocity and early latency, went clinically unnoticed. In this study, however, gains >0.6 were assumed as normal, although the cited reference (MacDougall et al. 2009) was using a greater cut-off value of 0.68, which, in addition, was based on previous search coil and not on vHIT recordings. In view of the “bump” artefact, which now is recognized to increase instantaneous gain in vHIT (MacDougall et al 2013a; MacDougall et al 2013b), a coil-based gain cut-off at 0.6 is too low and might have caused a considerable number of false negative results (Perez-Fernandez et al. 2012, Figures 1 and 3)."

In addition to slow-velocity refixation saccades, the presence of a spontaneous nystagmus (SN) might place an extra difficulty when interpreting the HIT, as it may be difficult to distinguish nystagmus quick phases from refixating corrective saccades during ipsilesional impulses since they share the same direction and kinematic characteristics (**supplementary video 3**).

This data suggests that vHIT is more than just the quantification of HIT, not only because it provides additional information, such as VOR slow phase and covert saccade's characteristics, but also due to methodological differences. With HIT performed with the examiner standing in front of the patient, the target is located at a much shorter distance, usually near the examiner's nose, and convergence may interfere with the VOR evaluation.

Also, vHIT analyses the head impulse characteristics and visually reports them to the examiner. Therefore, this system's feedback enables the examiner to learn how to produce normalized and more reproducible head impulses [though in clinical HIT, random rather than systematic head impulse amplitudes may help uncover covert saccades (Tjernström et al. 2012)], and discards impulses that do not match the minimum quality criteria, e.g., low velocity impulses that do not saturate the contralateral vestibular signal. Finally, with a minimum of 6 head thrusts to each side with vHIT, more impulses usually are generated with the vHIT than with the clinical HIT (Pérez-Fernández et al. 2012).

3.3. vHIT vs. caloric test.

When compared to vHIT, the caloric test presents a number of disadvantages when evaluating the angular VOR. The caloric test evaluates VOR in a frequency domain below the physiological range (0.003 Hz) (Formby and Robinson 2000), it induces a non-physiologic endolymphatic flow in the horizontal SCC due to a temperature gradient and it is characterized by considerable technique problems, such as failed irrigation, asymmetrical transmission of thermal energy or persistence of stimulation between irrigations and alertness. Also, it is a time-consuming test and it may cause significant discomfort to patients. Finally, deficit results don't supply cues to compensation, restitution or substitution mechanisms taking place. In contrast, vHIT evaluates the physiological high frequency range of the VOR in horizontal and vertical SCC planes (up to 5.0 Hz) (Jorns-Haderli et al. 2007). With instantaneous gain analysis (Aw et al. 1996), there is no cortical or slower ocular motor system interference, in contrast to the more recent *position gain* analysis (MacDougall et al. 2013b). The test is fast and well-tolerated, thus allowing re-testing. Also, the analysis of compensatory saccadic patterns provides insights into the compensation process (MacDougall and Curthoys 2012; Batuecas-Caletrio et al. 2013; Mantokoudis et al. 2014).

When bi-thermal caloric irrigation is set as gold standard for vestibular end-organ function, vHIT reaches low sensitivity scores to identify caloric weakness, particularly in non-acute patients. In addition, VOR gain asymmetry also correlates weakly with canal paresis (Blödow et al. 2014; Eza-Nuñez et al. 2014). However, in these studies, otoneurological clinical population cohorts tended, with some exceptions, to be heterogeneous with respect to the cause of vertigo and dizziness. Furthermore, patients with somatoform vertigo or

migraine with abnormal calorics have also been included (Mahringer and Rambold 2014; Eza-Nuñez et al. 2014), although abnormal canal parameters are not characteristic for these groups. Remarkably, only 11% and 15% of the above mentioned patients showed pathological vHIT, versus 90% for acute vestibular neuritis (Mahringer and Rambold 2014). Finally, there was also no correlation between the time course of caloric unilateral weakness and vHIT gain asymmetry during superior vestibular neuritis recovery, either at an individual or group level (Zellhuber et al. 2013).

In chronic UVL resulting from vestibular neuritis, vHIT has failed to detect 33% (Mahringer and Rambold 2014) and 22% (McCaslin et al. 2014) of the patients identified with bithermal caloric testing, thus discriminating normal from abnormal calorics with an overall diagnostic accuracy of 92% (McCaslin et al. 2014). Likewise, calorics have failed to identify 35% of patients with chronic UVL resulting from vestibular neuritis, as identified with impulses recorded with coils (Schmid-Priscoveanu et al. 2001). Furthermore, the caloric test is expected to be normal in lesions selectively affecting the vertical SCC function and, thus, is expected to fail in identifying vertical canal involvement, e.g., in acute inferior vestibular neuritis (Halmagyi et al. 2002) or posterior ampullary neuritis. In contrast, vertical vHIT should demonstrate in these cases a selective loss of posterior semicircular canal function (**Figure 7b**). In a recent study (Eza-Nuñez et al. 2014) that analysed the caloric response from each ear independently, 17% of patients presented normal vHIT and abnormal calorics, but 20% presented abnormal vHIT with normal calorics. While the former may be a common finding in non-acute stages of Ménière's disease (MD) (Park et al. 2005), the latter has been reported in 4% of vestibular schwannoma patients (Blödow et al. 2014).

In vestibular schwannoma, a model of complete unilateral vestibular deafferentation, caloric sensitivity (72%) was in fact higher than vHIT, whether hVOR or (horizontal plane) asymmetry ratio were considered (44% vs. 36%), suggesting that canal function may be substantially preserved at high accelerations in these patients. vHIT results also did not depend on tumour grade (Blödow et al. 2014).

With slower ($<150^\circ/\text{s}$) as well as faster ($>170^\circ/\text{s}$) peak head velocities, horizontal canal function may also be better preserved in BVL patients with MD (Kremmyda et al. 2014), as these showed significantly higher vHIT gains (regression, peak-velocity and position gain) than those with idiopathic and

aminoglycoside toxicity. Remarkably, no statistical difference was found in the results of caloric irrigation in these three groups (Kremmyda et al. 2014).

Not only the lack of vertical canal analysis and technical limitations, such as impulse velocity thresholds, but also the defining characteristics for a pathological vHIT may prove to be critical. A pathological vHIT has been defined differently, using a threshold of 0.60 (Eza-Nuñez et al. 2014) and 0.80 (Mahringer and Rambold 2014) for position gain or 0.70 for instantaneous gain averaging (McCaslin et al. 2014). Covert and overt saccades' presence also was considered pathologic, although no quantification of the saccade characteristics such as peak-velocity, amplitude or occurrence-rate was usually provided in order to differentiate from the low peak velocity and low occurrence rate of the overt saccades that also can be found in normal subjects (Blödow et al. 2013; Luis et al. 2014a) (**Table 2**). Nevertheless, the presence of saccades with similar characteristics and normal hVOR also have been associated with higher canal paresis in the caloric test (Pérez-Fernández et al. 2012).

In conclusion, the current available data suggests that the caloric test may present a higher sensitivity than vHIT in detecting vestibular schwannoma (Blödow et al. 2013), as probably in detecting MD during symptom-free stages. In MD, a VOR dissociation such as an increased VOR during the acute stage (Manzari et al. 2013b) may prove to be characteristic of this condition. Impulsive testing also may unveil central vestibular lesions where caloric testing yields normal results, such as in patients with neurodegenerative disorders and CANVAS (Wessel et al. 1998; Kremmyda et al. 2012). While it is still unclear whether vHIT and caloric dissociation is specific for disease, disease-stage or location, or if it just results from the test itself, given its different frequency testing domains, the complementary use of both neurophysiological tools is recommended. Thus a complete assessment of horizontal canal function needs both tests if one is normal.

3.4. vHIT vs. clinical scales.

3.4.1. DHI (Dizziness Handicap Inventory)

DHI (Jacobson and Newman 1990) is a clinical scale designed to assess the impact of dizziness on quality of life that has been adapted to several

languages and countries namely the Portuguese language from Portugal (Vaz Garcia et al, 2008). In a cohort of chronic UVL resulting from vestibular neuritis / labyrinthitis, no correlation was found between DHI score and vHIT outcome (McCaslin et al. 2014) (in this study, the vHIT was considered pathological if average instantaneous gain at 40, 60 and 80 ms after head impulse start was below 0.70 or if covert or overt saccades presented an occurrence rate over 50%). Nevertheless, in chronic UVL patients with deficient VOR gain after schwannoma surgery, a higher level of vestibular disability and handicap, as assessed with DHI, has been associated with a random *versus* an isochronous refixation saccade pattern in vHIT (Batuecas-Caletrio et al. 2013). This random refixation saccade pattern, moreover, has been associated with older age and more preserved pre-operative VOR function, as assessed with the caloric test (Batuecas-Caletrio et al. 2013). In a cohort of chronic BVL resulting from MD, aminoglycoside toxicity and idiopathic, DHI correlated negatively with gain (calculated at peak velocity and as a sum during the head impulse) but not with calorics (Kremmyda et al. 2014). Altogether, these studies add to the existing data of limited correlation of DHI with balance function tests, as this scale more closely may be associated with anxiety and depression symptoms.

3.4.2. SARA (Scale for the Assessment and Rating of Ataxia)

SARA is a validated clinical scale for cerebellar ataxia where gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test are quantified according to an impairment level (Schmitz-Hübsch et al. 2006). Although oculomotor function is not considered in this scale, a significant negative correlation has been found between VOR gain and SARA score in a cohort of patients with spinocerebellar and Friedreich's ataxia (Luis et al. 2014a). This raises the possibility of using VOR gain as a neurophysiological biomarker for disease severity in hereditary cerebellar ataxias (Gordon et al. 2014).

Table 3. Summary of the revised studies on vHIT comparative studies

Authors	Study type	Compared variable	Population size	Disease	Main Finding
MacDougall et al., 2009	Prospective, comparative and controlled	Search coils	Patients (n=8) Controls (n=8)	VN, unilateral and bilateral gentamicin vestibulo-toxicity	vHIT enables hVOR quantification and detects covert and overt saccades; hVOR is equivalent to search-coil data.
Agrawal et al., 2013	Prospective and comparative	Search coils	>70 yo subjects (n=6)	NA	hVOR gain and refixation saccades quantification is comparable to search-coil data. Correlation between vHIT and search-coil hVOR gain was 0.86.
MacDougall et al., 2013 PLOS	Prospective, comparative and controlled	Search coils	Patients (n=3), Controls (n=1)	Vestibular schwannoma, BVL, SCC plug	vHIT enables VOR quantification in horizontal and vertical SCC planes; data is closely comparable with coils.
MacDougall et al., 2013 Otol Neurotol	Prospective comparative and controlled	Search coils	Patients (n=3), Controls (n=1)	Vestibular schwannoma, idiopathic isolated SCC loss, BVL	vHIT enables VOR quantification in horizontal and vertical SCC planes.
Pérez-Fernández et al., 2012	Prospective and comparative	Clinical HIT	Patients (n=179)	VN, vestibular schwannoma	Clinical HIT identified 93% of normal vHIT patients but only 35% of abnormal vHIT patients; these were mostly patients with normal hVOR gain and refixation saccades.
Tjernström et al., 2012	Prospective and comparative	Clinical HIT	Patients (n=5)	VN, Vestibular schwannoma, BVL	The covert refixation saccades identified with vHIT may be identified with clinical HIT if random head amplitudes are generated.

Mahringer et al., 2013	Retrospective and comparative	Clinical HIT Calorics	Patients (n=172)	VN, pBPPV, MD, vestibular migraine, central vertigo, somatoform vertigo	Clinical HIT identified 93%/59% of normal and 72%/93% of abnormal vHIT patients in acute/non-acute disease. vHIT sensitivity to identify caloric unilateral weakness was 63%/33 % in acute/non-acute disease.
Zellhuber Et al., 2013	Retrospective and comparative	Calorics	Patients (n=19)	VN	VOR asymmetry and caloric weakness time course during VN recovery were not correlated at group or individual level.
Blödow et al., 2014	Retrospective and comparative	Calorics	Patients (n=69)	Vestibular schwannoma	The sensitivity of hVOR /gain asymmetry to identify patients was 36%/44% vs. 72% for calorics. In 4% of the patients with normal calorics results, the vHIT was abnormal. vHIT results did not depend on tumour grade.
Eza-Nuñez et al., 2014	Retrospective and comparative	Calorics	Patients (n=123)	VN/Labyrinthitis, vestibular schwannoma, BPPV, MD, vestibular migraine, Posttraumatic, otosclerosis, serous otitis	vHIT gain sensitivity in identifying caloric unilateral weakness was 59%, specificity was 66%. Correlation between canal paresis and hVOR gain asymmetry was 0.67.
McCaslin et al., 2014	Prospective and comparative	Calorics DHI	Patients (n=115)	VN / labyrinthitis	vHIT gain sensitivity in identifying caloric unilateral weakness was 78%. DHI score was not correlated with vHIT (or calorics).
Batuecas-Caletrio et al., 2014	Retrospective and comparative	DHI	Patients (n=49)	vestibular schwannoma (postoperative)	hVOR gain is reduced ipsilesionally after surgery; vHIT with random refixation saccades' pattern is associated with higher DHI score.

BPPV: benign paroxysmal positional vertigo; BVL: Bilateral Vestibular Lesion; DHI: Dizziness Handicap Inventory; HIT: Head impulse test; hVOR: VOR gain in the plane of the horizontal SCC; MD: Ménière's disease; NA – not applicable; pBPPV: BPPV of the posterior SCC; SCC: semicircular canal; vHIT: video head impulse test; VN: vestibular neuritis; VOR: vestibulo-ocular reflex.

4. Clinical Utility.

In this section we review the studies that provide data on the diagnostic utility of vHIT neurophysiological recordings.

4.1. Acute Vestibular Lesion (AVL).

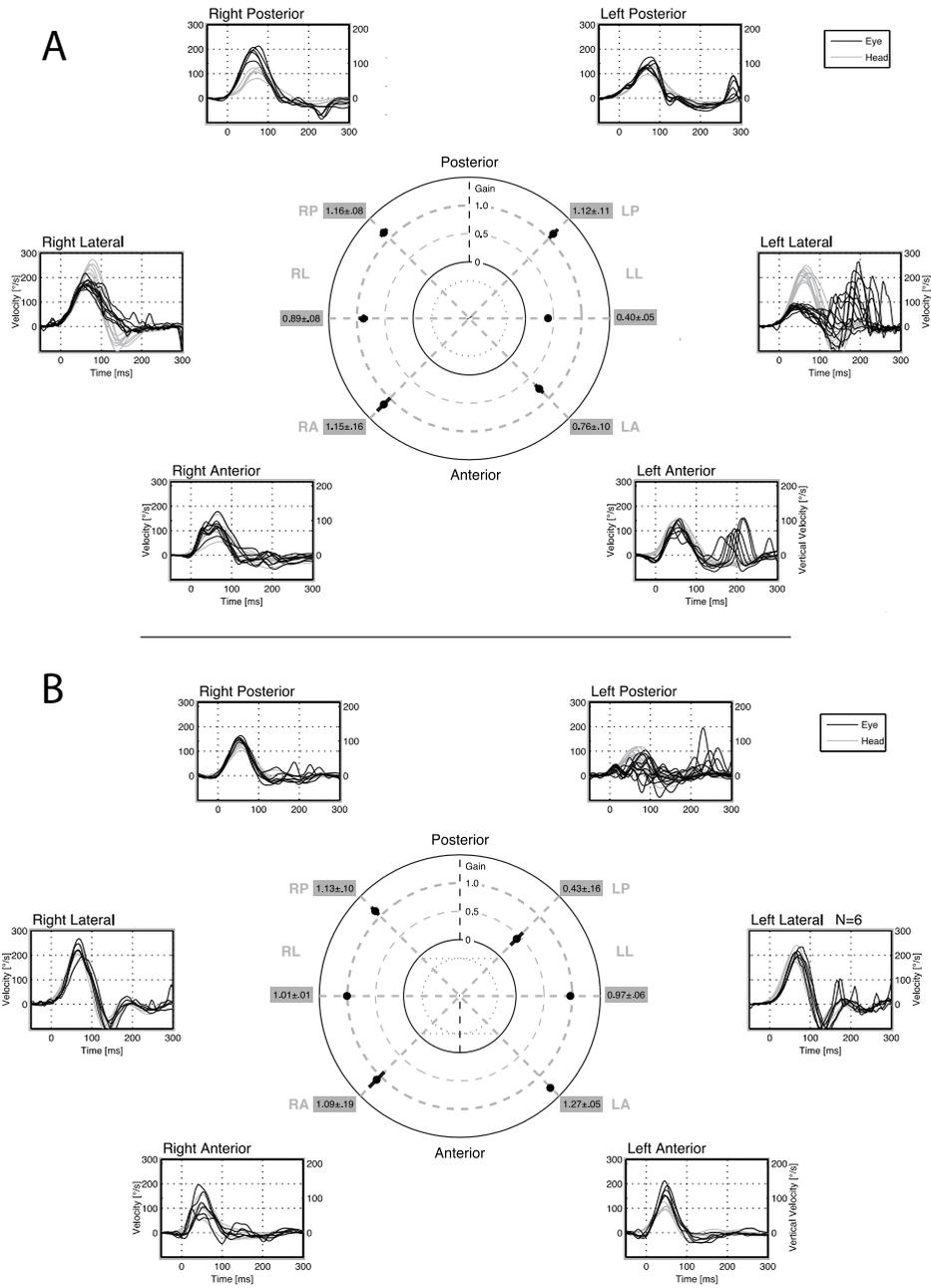
Table 4 summarizes the vHIT studies on acute vestibular lesion.

The most frequent cause of an acute vestibular syndrome is a peripheral UVL (Hotson and Baloh 1998). An acute unilateral vestibular deficit in vestibular neuritis or labyrinthitis may be identified with the vHIT as a non-compensatory eye velocity trajectory during ipsilesional impulses along the plane of the involved canal(s) (Manzari et al. 2011b; Walther and Blödow 2013; Manzari et al. 2013b) (**Figure 4a** and **Figure 4c, day 1**). Vestibular neuritis, in most cases, does not cause complete vestibular loss but involves the superior vestibular nerve (Fetter and Dichgans 1996; Aw et al. 2001) that carries primary afferents from the anterior and lateral ampullae (**Figure 7a**). Separate testing of posterior SCC planes with vHIT allows identification of inferior vestibular nerve involvement, since the inferior vestibular nerve carries afferents selectively from the posterior *ampullae* (**Figure 7b**). Of special mention, a selective isolated posterior SCC lesion has been described after cochlear implant electrode array misplacement (Batuecas-Caletrio et al. 2014). Involvement of the horizontal SCC with normal superior SCC responses (Aw et al. 2001) also has been described in the context of superior vestibular neuritis, but may suggest isolated ampullary nerve neuritis (Walther and Blödow 2013).

VOR gain and asymmetry level estimation further provides information regarding the severity of the lesion, with lower VOR gains and higher asymmetries associated with more severe lesions. The VOR during impulses towards the healthy, contralesional side also may present lower values than healthy controls, because at high accelerations, the contribution of the ipsilesional canal through the VOR inhibitory pathway is defective and, therefore, does not add to the contralesional VOR excitatory pathway (Halmagyi et al. 1990a; Aw et al. 1996a; Palla and Straumann 2004).

In an UVL acute stage, the gaze position error resulting from a non-compensatory VOR slow-phase is higher, and refixating saccades also present higher peak-velocity, amplitude and occurrence-rate during and/or after the head impulses, with the covert saccades substituting the dynamic vestibular loss (Macdougall and Curthoys 2012). During the recovery period, the slow phase progressively regains and the catch-up saccades peak-velocity, amplitude

Figure 7 3D vHIT along the horizontal and vertical SCC planes



A- Left Superior vestibular neuritis. With head impulses to the left horizontal and anterior SCCs the eyes do not compensate for the head. The vestibulo-ocular reflex (VOR) is deficient and the patient makes compensatory

[Figure 7 A (Cont.)] refixation saccades. Note that AQEM are triggered when the head is turned to the contralesional side along the (right) horizontal and posterior canal.

- B- Left inferior vestibular neuritis. With head impulses to the left posterior SCC the eyes do not compensate for the head, the vestibulo-ocular reflex (VOR) is deficient and the patient makes compensatory refixation saccades..

and occurrence rate diminish (**Figure 4c**). In case of non-recovery, e.g., after schwannoma surgery, refixating saccades latency also decline with time, so that these may be difficult to identify clinically (Mantokoudis et al. 2014).

The presence of a (paretic) SN of peripheral origin may be noticed in a vHIT plot by identifying AQEM which are triggered during contralesional impulses (Luis et al. 2014c) (**Figure 4c**). AQEM share the direction of the head, i.e., the opposite direction of the VOR slow phase and may represent the nystagmus fast phases modulated by the short high-amplitude increase in the level of persisting vestibular imbalance generated by contralesional impulses (Luis et al. 2014c). In AVL of central origin, AQEM are absent.

It has been reported that some patients with AVL of peripheral aetiology show normal vHIT but abnormal vestibular evoked myogenic potentials (VEMP), supposedly due to otolith dysfunction (Manzari et al. 2012b; 2012a). Still, head impulse velocity was too slow to make use of Ewald's 2nd law (Halmagyi et al. 1990; Weber et al. 2008a,b) and, therefore, to unmask an asymmetry (Luis et al. 2014d). This might have (mis)lead to a false-negative vHIT outcome, as was demonstrated in a patient with left-side mastoidectomy (Machner et al. 2013). Further one of the cases was not considered pathological (Manzari et al. 2012a) although there was a high occurrence rate of quick eye movements and both the gains (1.35 and 1.14) and the asymmetry were beyond the normative ranges.

In Ménière's disease acute attack, hVOR has also been reported to present normal to high gain values ipsilesionally, but with enhanced ocular VEMP (Manzari et al. 2013b). In contrast, in a Lermoyez Syndrome case report, hVOR remained equally low in the ipsilesional ear during the acute attack, but decreased significantly in the contralesional ear (Manzari et al. 2011a). A displacement of the horizontal SCC cupula towards the utricle was the assumed reason, as an ipsilesional head impulse would generate an unchanged VOR when compared to the non-acute stage. In contrast, a contralesional head impulse would generate a decreased VOR, due to a decreased ipsilesional inhibitory response.

In a patient with AVL, a reversible saturation of the eye velocity trajectory also has been hypothesized to be caused by a constant deflection of the cupula, possibly resulting from a spontaneous plugging of the horizontal SCC (Luis et al. 2013) (**Figure 4b**). This velocity profile, also demonstrated in a surgical canal plug (Macdougall et al. 2013b), immediately recovered after a liberatory maneuver, thereby documenting a high-frequency VOR hypofunction during benign paroxysmal positional vertigo (BPPV) with spontaneous nystagmus. In contrast, in superior SCC BPPV patients, VOR gain was normal in both the horizontal and vertical canals (Pérez-Fernández et al. 2014). In this condition, though, an otoconial plug is not the supposed biomechanism (Yacovino et al. 2009; Luis et al. 2014e).

The correct identification of the AVS patients resulting from central, cerebellar or brainstem lesions is of great importance as they are at risk of developing a life-threatening condition related to posterior fossa strokes. In the absence of neurological signs and symptoms, the normal HIT was shown to be the best predictor of a CNS dysfunction in an AVS (Newman-Toker et al. 2008; Kattah et al. 2009) (**supplementary video 4**). In accordance with the HIT results, vHIT testing of posterior inferior cerebellar artery (PICA) strokes, causing AVS, show normal hVOR. Still, anterior inferior cerebellar artery (AICA) strokes may show deficient slow phases (**Figure 8c**), possibly as a result of combined cerebellar and labyrinthine infarctions (Newman-Toker et al. 2013). Isolated cerebellar flocculus lesions also have been described as affecting VOR gain bilaterally (Park et al. 2013). In such patients, clinicians need to interpret an abnormal vHIT in light of no other contradictory information, e.g., impaired pursuit and or severe ataxia. Although these patients show SN, interestingly, they may not present anti-compensatory, but only compensatory saccades (Luis et al. 2014c).

Finally, the combination of SCC lesions also may have topographic value, as was reported in a patient with an inferior peduncle glioma and a selective lesion of both posterior and horizontal semicircular canals and preserved responses in the anterior canals (Zuma e Maia and Luis 2014).

In conclusion, vHIT in AVL provides information regarding the side and severity of the lesion, the presence of spontaneous nystagmus and topodiagnosis information as well as clues on the compensatory mechanisms and recovery processes taking place. The vHIT evaluation allows not only the non-invasive documentation of the pathological process, with full or partial recovery, but also may deliver valuable information for the treatment adjustment.

Table 4. Summary of the revised studies on acute vestibular lesion

Authors	Study type	Population size	Disease	Main Finding
Manzari et al., 2011	Case report	1	VN	vHIT identified a non-compensatory hVOR and compensatory saccades, abnormal oVEMP and calorics; later restoration with compensatory VOR slow phase, normal calorics and normal oVEMP.
Manzari et al., 2011	Retrospective	Patients (n=2)	VN MD	In the acute stage and ipsilesionally the VN patient presented reduced hVOR and reduced oVEMP, the MD patient showed increased hVOR gain and increased oVEMP.
Manzari et al., 2012	Case report	1	Labyrinthitis	Horizontal SN patient (adult) with normal horizontal and vertical VOR gain and calorics but asymmetrical oVEMP.
Manzari et al., 2012	Case report	1	AVL	Horizonto-torsional SN patient (child) with normal hVOR but asymmetrical cVEMP and oVEMP.
Manzari et al., 2012	Case report	1	Lermoyez syndrome	hVOR decreased significantly in the acute attack in the contralesional side but remained low in the ipsilesional side.
Luis et al., 2013	Case report	1	hBPPV (SCC plug)	vHIT demonstrated a reversible deficiency of the cupular-endolymph high-frequency system dynamics.
Walther et al., 2013	Prospective	Patients (n=20)	VN	(3D) vHIT together with VEMP allows the topologic diagnosis of complete, superior, inferior and ampullary VN.

Walther et al., 2013	Case report	1	MD	vHIT quantifies the time-dependent reduction of hVOR gain and overt and covert saccades after intra-tympanic gentamicin.
Batuecas-Caletrio et al., 2013	Case report	1	Labyrinthitis	vHIT allowed the diagnosis of a posterior canal lesion due to a misplaced electrode array after cochlear implantation.
Newman-Toker et al., 2013	Prospective and controlled	Stroke patients (n=6) Non-stroke patients (n=6)	AVS	Diagnostic accuracy of hVOR plus direction changing nystagmus and skew deviation (quantitative HINTS) for central versus peripheral vestibular lesion was 100%.
Mantokoudis et al., 2014	Prospective	Patients (n=5),	Post-operative Vestibular schwannoma	hVOR gain is reduced on both the ipsi- and contra-lesional side immediately after surgery; refixation saccades latency declines with time and may therefore be difficult to identify clinically.
Pérez-Fernández et al., 2014	Retrospective	Patients (n=12)	aBPPV	VOR gain is normal in horizontal and vertical planes.
Luis et al., 2014	Retrospective	Patients (n=43)	VN, MD, vestibular neurectomy, vestibular migraine, stroke	The presence of AQEM in AVS increases the diagnostic accuracy.

aBPPV (BPPV of the anterior SCC); AQEM: anti-compensatory quick-eye movements; AVL: Acute Vestibular Lesion; AVS: acute vestibular syndrome; BPPV (benign paroxysmal positional vertigo); cVEMP: cervical vestibular evoked myogenic potential; HINTS: HIT plus direction changing nystagmus and skew deviation; hVOR: VOR gain in the plane of the horizontal SCC; MD: Ménière's disease; oVEMP: ocular vestibular evoked myogenic potential; pBPPV (BPPV of the posterior SCC); SCC: semicircular canal; SN: spontaneous nystagmus; vHIT: video head impulse test; VN: vestibular neuritis; VOR: vestibulo-ocular reflex.

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4.2. Chronic Peripheral Vestibular Lesion (CVL).

Table 5 summarizes the vHIT studies on chronic vestibular lesion.

After a vestibular lesion, some patients will maintain a vestibular deficit. The aetiology may be surgical (Blödow et al. 2014; Mantokoudis et al. 2014), chemical (aminoglycosides) (Walther et al. 2013), infectious or inflammatory, neoplastic or idiopathic. More than acute, CVL patients may be missed without quantified impulsive tests (**Figure 5b**). In some unilateral patients, but also in BVL patients, isochronously locked covert saccades may substitute the VOR so effectively that almost no overt saccades or visuo-vestibular symptoms are triggered, both clinical indicators of gaze position error. Therefore, the evaluation of both the slow phase and QEM, vHIT allows an accurate vestibular evaluation in patients that, otherwise, could result in a false negative with the non-quantifying, clinical HIT (MacDougall et al. 2009; Blödow et al. 2013; Macdougall and Curthoys 2012; Manzari et al. 2013a).

Not only compensatory, but also AQEM may be noticed in CVL, particularly during the head impulse (covert AQEM; CAQEM) (Heuberger et al. 2014). As with AVL patients, AQEM (Luis et al. 2014c) also seem to result from a gain asymmetry, increased during the contralateral impulses, and also point to a nystagmus quick phase mechanism. Similar to AQEM, they point to a peripheral origin and, therefore, can contribute to topodiagnosis, e.g., helping differentiate MD from vestibular migraine (Heuberger et al. 2014).

Table 5. Summary of the revised studies on chronic vestibular lesion.

Authors	Study type	Population size	Disease	Main Finding
MacDougall et al., 2009	Prospective, comparative and controlled	Patients (n=8) Controls (n=8)	VN, unilateral and bilateral gentamicin vestibulo-toxicity	vHIT enables hVOR quantification and detects covert and overt saccades; hVOR is equivalent to search-coil data.
Blödow et al., 2012	Prospective, comparative and controlled	Patients (n=117), Controls (n=20)	VN, vestibular schwannoma, MD, BVL	vHIT enables hVOR quantification and detects covert and overt saccades; hVOR gain (0.96 ± 0.08) is comparable to search-coil data.
Manzari et al., 2013	Retrospective	Patients (n=2)	VN	One patient recovered hVOR (and cVEMP but not oVEMP); the other patient did not recover hVOR but triggered covert and overt saccades.
Heuberger et al., 2014	Retrospective	Patients (n=266)	MD, Vestibular Migraine, vestibular paroxysmia, BVL, UVL, other	Covert AQEM are more common in peripheral vestibular and could help differentiate MD from vestibular migraine.

AQEM : anti-compensatory quick eye movements; BVL: Bilateral Vestibular Lesion; cVEMP: cervical vestibular evoked myogenic potential; hVOR: VOR gain in the plane of the horizontal SCC; MD: Ménière's disease; oVEMP: ocular vestibular evoked myogenic potential; SCC: semicircular canal; SN: spontaneous nystagmus; UVL: Unilateral vestibular lesion; vHIT: video head impulse test; VN: vestibular neuritis; VOR: vestibulo-ocular reflex.

4.3. Central vestibular lesions.

Table 6 summarizes the vHIT studies on central vestibular lesions.

Although VOR usually is considered to be normal in patients with vestibular symptoms due to central nervous system (CNS) disorders (Newman-Toker et al. 2013), several studies have described significant changes in VOR function in patients with inherited ataxias (Gordon et al. 2003; Yoshizawa et al. 2004; Fahey et al. 2008; Zeigelboim et al. 2011), non-inherited ataxias (Kremmyda et al. 2012) and cerebellar infarction (Park et al., 2013), so that, altogether, bedside HIT may result in a risk of false-positive results in diagnosing peripheral vestibular deficits (Kremmyda et al. 2012).

Recent evidence from patients with non-inherited cerebellar ataxia and bilateral vestibulopathy further suggests that patients with pure central and mixed central and peripheral lesions may be discriminated based on the characteristics of VOR changes (Kremmyda et al. 2012). Furthermore, in a cohort of patients with spinocerebellar (SCA) and Friedreich ataxia (FA), vHIT has shown to provide phenotypic information that differentiated these autosomal ataxias and, therefore, could serve as a strategy to orient genetic diagnosis (Luis et al. 2014a). Patients with SCA3 and FA showed bilateral defective slow phases (Figure 9), but only the first showed an increased latency, and only the second triggered covert saccades (Luis et al. 2014a). In Charcot-Marie-Tooth disease type 4C, a hereditary neuropathy, a bilaterally reduced hVOR with overt refixating saccades also has been demonstrated with the vHIT (Pérez Garrigues et al, 2014).

Table 6. Summary of the revised studies in central vestibular lesion.

Authors	Study type	Population size	Disease	Main Finding
Szmulewicz Et al., 2011	Retrospective	Patients (n=27)	CANVAS	Horizontal and vertical VOR gain is bilaterally low with catch-up saccades.
Petersen et al., 2013	Case report	1	CANVAS	Bilaterally reduced hVOR with overt catch-up saccades.
Luis et al. 2013	Prospective and controlled	Patients (n=32) Controls (n=40)	SCA 1, 2 and 3, FA	vHIT shows bilaterally reduced hVOR and increased VOR latency in SCA3 and FA, with a negative correlation between hVOR and disease severity. Only SCA3 triggered covert saccades.
Baxter et al., 2014	Case report	1	Turner Syndrome	hVOR was bilaterally low with covert saccades.
Pérez-Garrigues et al., 2014	Prospective and controlled	Patients (n=10) Controls (n=10)	Charcot-Marie-Tooth disease type 4C	Bilateral low hVOR or catch-up saccades were present in all patients; no correlation with calorics or galvanic.
Wu et al., 2014	Prospective	Patients (n=26)	CANVAS	hVOR was used to quantify BVL in 18 patients

Luis et al. 2014	Prospective and controlled	Patients (n=18) Controls (n=40)	Huntington's disease	vHIT shows normal VOR latency and hVOR. No differences were found between pre-symptomatic and symptomatic patients.
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BVL: Bilateral Vestibular Lesion; CANVAS: cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome; FA: Friedreich ataxia; hVOR: VOR gain in the plane of the horizontal SCC; SCA: spinocerebellar ataxia; SCC: semicircular canal; vHIT: video head impulse test; VOR: vestibulo-ocular reflex.

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CHAPTER II

RATIONALE AND OBJECTIVES

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Head impulse gain and quick-eye movement analysis

Since the pioneer work of Swee Aw (1996), who explored the human VOR in response to head impulses in normal, UVL and selective canal occlusion subjects, much interest has been directed to the analysis of the VOR slow phase instantaneous gain. but not of gain dynamics or QEM. This was particularly puzzling regarding QEM as the clinical HIT analysis relies in the identification of a type of QEM – overt saccades. Although quick eye movements were indeed present in scleral search coil recordings during head impulses they were for years systematically disregarded. In short, they were taken as automatic responses to vestibular lesions, deprived of pathologic or even physiologic interest: all the attention was directed to VOR gain. With the introduction of vHIT the number of recordings and explored patients but also the doubts regarding the interpretation of results raised so quickly that it became clear that VOR instantaneous gain analysis was not enough to answer these questions and that VOR gain dynamics and QEM were worth investigating.

Our first goal was to establish normative data across control subjects not only for VOR gain(s) but also for QEM characteristics, namely latency, peak-velocity, occurrence-rate and direction. The first subjects that could benefit from this were the ones presenting normal range VOR gain with QEM, as there is no consensus regarding the normality or abnormality of those responses.

Our second goal was to explore patients diagnosed with acute vestibular syndrome with spontaneous nystagmus of peripheral and central origin looking for vHIT characteristics that could have topodiagnostic value.

Finally we explored patients with hereditary neurodegenerative disorder with known involvement of vestibular pathways (spinocerebellar ataxia type 1, 2 and 3 and Friedreich ataxia,) and without involvement of vestibular pathways (Huntington's disease).

I. vHIT evaluation in normal subjects

1. Normal Vestibulo-ocular Reflex Gain and Quick Eye Movements with Horizontal Head Impulses

Normative data for VOR slow-phase instantaneous gain was already available in the literature for coils but not for the vHIT. Most of the pioneer papers just used the data available for coils, although the methods for the calculation of gain could be, in some cases, dramatically different, e.g. calculated at peak-velocity for coils and calculated as position gain, for vHIT. Additionally, with the introduction of regression gain calculation, gain asymmetry and gain dynamics (Luis et al 2013) normative data for these gain calculations was also needed.

Regarding quick eye movements, these have been majorly ignored with coil HIT evaluation, so absolutely no normative data was available. For some, their presence was simply considered pathologic. For others their presence, role or significance was inexistent: all the attention should be directed to the slow phase gain

The purpose of this study was therefore to establish normative data across control subjects aged 14 to 79 years and to establish a control group.

II. Topodiagnosis in Acute Vestibular Syndrome patients

In 1993 Vaz Garcia F. and colleagues conducted a study in Santa Maria Hospital Emergency Room in Lisbon, Portugal (Vaz Garcia F, Marques P. Neurotology Newsletter. 1996;2(2):75-79). In this study ca. 1% of a total 159.606 patients attending the Emergency Room did so for acute dizziness and vertigo as the main complaint. Surprisingly, about 80% of these patients left the hospital without any diagnose or with “vertiginous syndrome” as the discharge diagnose.

Although a peripheral vestibular lesion is the most frequent cause for an acute vestibular the identification of those resulting from central lesions,

namely strokes, can be life saving. Differentiating central from peripheral origins of spontaneous nystagmus (SN) is still a challenge. Nystagmus characteristics, other oculomotor findings, and the head impulse test each are not sufficient to make the diagnosis and are commonly used in combination (Cnyrim et al. 2008) often complemented with imaging. In acute vestibular syndrome, i.e., SN with vertigo, nausea, vomiting, and unsteadiness, assessing gaze-evoked nystagmus, skew deviation, and head impulses quite accurately differentiates strokes from peripheral vestibular disorders. (Kattah et al. 2009). Peripheral vestibular lesions should present defective eye velocity profiles during head impulses, thereby generating compensatory catch-up saccades, identifiable at a clinical level (overt saccades) while central lesions should present compensatory eye velocity profiles during head impulses and therefore no catch-up saccades should be identified at a clinical level. Quantifying the vestibulo-ocular reflex (VOR) gain by the video head impulse test (vHIT) (Bartl et al. 2009; MacDougall et al. 2009), further increases diagnostic accuracy. (Newman-Toker et al. 2013). However, performing vHIT together with oculomotor tests requires expertise not always available.

During the early use of the vHIT in the evaluation of AVS patients we noted that while most central vestibular patients presented compensatory VOR slow phases, some AICA strokes did present defective slow phases, and sometimes bilaterally defective slow phases. We also noted that while peripheral vestibular patients with spontaneous nystagmus systematically presented anti-compensatory quick eye movements (AQEM) during contralesional impulses, central patients with spontaneous nystagmus did not. In the first study we assessed the diagnostic accuracy of both the slow phase gain as well as these AQEM to differentiate peripheral from central vestibular patients with acute vertigo with acute spontaneous nystagmus.

Additionally, we present one case report (Luis et al. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials. *Otol Neurotol.* 2013;34(4):743-7) where we noted a particular eye movement velocity profile during ipsilesional impulses associated with a SCC plug as well as a particular VEMP recovery pattern. This was the first study published in collaboration with the Munich group, namely with Thomas Brandt and Erich Schneider as co-authors. This paper originated particular controversy (Curthoys IS, Manzari L. Commentary on Luis et al "Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular

evoked myogenic potentials. *Otol Neurotol.* 2014;35(2):377-9) and an extended review and argumentation (Luis et al. Reply to the Commentary on Luis et al. "Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials". *Otol Neurotol.* 2014;35(2):379-83).

Altogether we aimed at investigating the value of VOR parameters, namely VOR regression and VOR dynamics as well as QEM and AQEM parameters in the topodiagnosis of acute vestibular lesion patients.

1. Anticompany quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus

Looking for a simple single sign of peripheral disease in vHIT, we noticed quick eye movements in the direction of the head movement in patients with peripheral, but not central, aetiologies of SN after their head was moved to the opposite side of the lesion (see movie 5). Here, we retrospectively assess the diagnostic accuracy of these anticompany quick eye movements (AQEM) as well as the VOR slow phase gain to differentiate peripheral from central vestibular disorders.

Movie 5. Ipsilesional and contralesional head impulses slow-motion-video in a patient with left vestibular neuritis and right spontaneous nystagmus.

With head impulses to the left (lesion side) the eyes do not compensate for the head and the patient makes a compensatory refixation saccade. When the head is turned to the right (contralesional side), anticompany quick eye movements (AQEM), i.e. eye movements in the direction of the head movement can be observed. A tone has been added to the video with each SN fast-phase, as well as a higher-pitch tone with AQEM for clearer identification. Video runs at 25, 10 and 5 % of the original speed.

2. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials

Benign paroxysmal positional vertigo (BPPV) is caused by otoconial debris that dislodges from the utricular macula and precipitate into the semicircular canals (SCC), thereby disturbing the endolymph flow during head movement. The debris can also fall into the ampulla, making the cupula sensitive to gravity (Brandt et al., 1993). There are two types of BPPV with horizontal nystagmus (hBPPV). The clinically more frequent type with geotropic nystagmus is supposedly caused by canalolithiasis of the long SCC arm, whereas the less frequent hBPPV, characterized by apogeotropic horizontal nystagmus during the Pagnini-McClure maneuver, is thought to be caused either by canalolithiasis of the SCC short arm or by cupulolithiasis. Both types can convert into the other (Steddin et al., 1996). Patients usually have a history of transient or persistent positional vertigo, but can present with (pseudo)-spontaneous vertigo and pseudo-spontaneous nystagmus (Asprella Libonati et al. 2008; Brevern et al., 2001) due to cupulolithiasis or spontaneous canal plugging.

The main goal of the vestibulo-ocular reflex (VOR) is to maintain clear vision by retinal image stabilization of the visual surroundings, particularly important during rapid head movements, quantitatively assessed with the video head-impulse test (vHIT) (MacDougall et al, 2009; , Bartl et al., 2009). The otolithic-ocular reflex is also an integral part of the VOR. This is thought to be evaluated by ocular vestibular evoked myogenic potentials (oVEMPs) in the same way that the vestibulocollic reflex can be accessed through cervical vestibular evoked myogenic potentials (cVEMPs) (Rosengren et al., 2010).

We report on a case that challenges the common belief that VEMPs are evoked by otolith stimulation only and document for the first time a high-frequency VOR hypofunction during BPPV.

III. Topodiagnosis in non-acute vestibular lesions

Most studies on impulsive VOR have studied the horizontal push-pull plane, along the horizontal SCC, in accordance with the clinical Head Impulsive, caloric stimulation and rotary chair. Still, the vertical planes may also be studied with the vHIT. These planes are the LARP (along the left anterior and right posterior SCC), and RALP (along the right anterior and left posterior SCC). Although vertical plane evaluation still presents significative challenges and technical issues, they may present diagnostic and topographic value in lesions selectively affecting the vertical SCC function, e.g., after inferior vestibular neuritis (Halmagyi et al. 2002) or posterior ampullary neuritis, where vHIT should demonstrate a selective loss of vertical canal function. This information is also relevant for topodiagnostic purposes in patients with non-acute vestibular lesions.

1. Inferior peduncle lesion presenting with bilaterally impaired vestibular responses to horizontal and posterior head impulses

Here we report an anecdotal combination of SCC high frequency VOR lesion in an inferior cerebellar peduncle lesion (Maia F, Luis L. Inferior peduncle lesion presenting with bilaterally impaired vestibular responses to horizontal and posterior head impulses. *Laryngoscope*. 2015, in print).

IV. Vestibular lesion in hereditary neurodegenerative disorders

Although the vestibulo-ocular reflex (VOR) is usually considered to be normal in patients with vestibular symptoms due to central nervous system (CNS) disorders (Newman-Toker et al. 2013), several studies have described significant changes in VOR function in patients with inherited ataxias (Gordon et al. 2003; Yoshizawa et al. 2004; Fahey et al. 2008; Zeigelboim et al. 2011) and more recently in cerebellar floccular infarction (Park et al. 2013). Recent

evidence from patients with non-inherited cerebellar ataxia and bilateral vestibulopathy further suggests that patients with pure central and mixed central and peripheral vestibular lesions may be discriminated based on the characteristics of VOR changes (Kremmyda et al. 2012).

In the present studies, we aimed at investigating the topodiagnostic value of vHIT in particular hereditary neurodegenerative disorders, as some are known to present vestibular involvement and at different levels, while others have no known involvement of the vestibular pathways.

1. Vestibulo-ocular reflex dynamics with head-impulses in Huntington's disease

No vestibular involvement is known in Huntington's disease, but only the lower VOR frequencies have been tested (calorics and rotary chair). We therefore aimed at investigating if higher VOR testing frequencies were also unaffected.

2. Vestibulo-ocular reflex dynamics with head-impulses in hereditary cerebellar ataxias

Clinically differentiating the different types of cerebellar ataxias can be difficult, as there is often an overlap in neurological signs and symptoms. Although the diagnosis of inherited ataxias is ultimately genetic, this usually means an extensive and expensive process that may postpone the beginning of treatment and of genetic counselling. This justifies the search for distinct clinical signs that may potentially help orient molecular diagnosis.

Though at different levels, vestibular involvement is known in Machado Joseph's disease (SCA3), SCA1, SCA2 and Friedreich ataxia. We hypothesised that vHIT could contribute to the identification of different oculomotor phenotypes, disease-specific and disease-stage specific biomarkers to guide genetic diagnosis. Additionally we wanted to better understand the neurophysiologic basis for VOR control when different levels are affected in vestibular system, and therefore contribute not only for topodiagnosis but also for better therapy and rehabilitation approaches.

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CHAPTER III

TECHNICAL AND METHODOLOGICAL ASPECTS

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Several technical methodological aspects were common to all the experiences, such as: (1) vHIT recording; (2) the general experiences conditions; (3) data analysis; and (4) ethical approval. For simplicity, and to avoid repetition, these general technical aspects are described below.

1. vHIT recording.

A detailed description of the technical methodological aspects related to vHIT recording used in these studies was previously presented in Chapter I (see pp. 42-51).

Briefly, horizontal head impulses were recorded with the EyeSeeCam (Munich, Germany), the camera mounted for left eye recording. The system was first calibrated by having the patient fixate at luminous dots projected by a head-fixed laser at predefined horizontally and vertically 8.5° angles.

VOR was obtained by manually delivering at least six valid high velocity ($150\text{-}300^\circ/\text{s}$) and low amplitude ($10\text{-}20^\circ$) head impulses in yaw and to each side, unpredictable as regards time and direction, while patients were asked to fixate a printed dot on a white board at 140 cm distance on the midline and at eye level

2. General experiences' conditions and procedures.

Patients were seated on the examination chair, relaxed, in a dimly lit room with constant temperature (24°C). They were instructed not to speak and to remain calm and relaxed during the experiments. All neurophysiological studies were performed under the same experimental conditions and with the same equipment.

3. Data analysis.

Data analysis was performed offline. Head impulses were detected with a velocity criterion (Halmagyi et al. 1990; Glasauer et al. 2004). The start of the

impulse was defined at a velocity threshold of $20^\circ/\text{s}$ and end of the impulse was defined when head velocity crossed zero again.

VOR latency was estimated as the minimal difference between head- and eye-velocity from head impulse start until reaching $70^\circ/\text{s}$ (Halmagyi et al. 1990; Aw et al. 1996).

VOR_r gain was estimated as the median of the ratio of eye and head velocity during 35-45 (VOR₄₀), 55-65 (VOR₆₀) and 75-85 ms (VOR₈₀) after head impulse start and as head-velocity to eye-velocity linear regression (Aw et al. 1996). The side-to-side quotient defined as the asymmetry index between sides (Schmid-Priscoveanu et al. 2001). If there were no differences in VOR gain between sides neither in healthy subjects nor in patients ($p \geq 0.05$ for all comparisons; paired T Test), data from both sides was pooled for group analysis. To explore VOR dynamics we determined the instantaneous VOR gain estimated as the median of the eye and head velocity ratio during 35-45, 55-65, and 75-85 ms (VOR₄₀, VOR₆₀ and VOR₈₀) after head impulse start.

Catch-up saccades were defined as quick eye movements (peak velocity over $30^\circ/\text{s}$ above slow-phase baseline velocity) triggered during (covert) or after (overt) the head impulse. Saccade start was at $10^\circ/\text{s}$, latency was the difference between head impulse start and the first catch-up saccade start for each subject. Catch-up saccade occurrence rate was the percentage of head impulses with catch-up saccades.

4. Ethical approval.

All subjects gave their informed consent for the studies, which were approved by the Ethics Committees of the Hospital Clínic of Barcelona and Lisbon Faculty of Medicine and Centro Hospitalar de Lisboa Norte. Before testing, each subject was given verbal and written information as to the nature and rationale of the test procedure, outlining the risks and exclusion criteria.

CHAPTER IV

CLINICAL STUDIES

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I. vHIT evaluation in normal subjects

1. Normal Vestibulo-ocular Reflex Gain and Quick Eye Movements with Horizontal Head Impulses

VOR data with impulses along the horizontal was obtained for 40 subjects aged 14 to 79 years (41.10 ± 16.6 years; women: 55%) with no previous form of brain disorder, inner ear dizziness or vertigo or restricted neck movement (**Table 7**). The VOR latency was -2.3 ± 2.1 ms. The average VOR gain was 0.94 ± 0.08 when calculated as a linear regression in the first 100 ms after head impulse start. The lower limit of the normal range VOR gain was 0.79 (2SD below mean). The lower limit of the normal range regression VOR gain was 0.78 (2SD below mean). The asymmetry level for regression gain was 3.13 ± 2.00 . No covert saccades were present. Overt saccades were present in 50% of the evaluated subjects, with $14.4 \pm 20.1\%$ occurrence rate, 174.8 ± 52.4 ms latency and 82.5 ± 43.4 °/s peak velocity. The occurrence rate for anti-compensatory quick eye movements was $0.3\% \pm 1.1\%$.

Table 7. VOR gain and QEM results in normal subjects

Population size	hVOR; cutoff					Saccades		
	VOR ₄₀	VOR ₆₀	VOR ₈₀	VOR _r	Asymmetry (ms)	latency	peak-velocity	occurrence
n=40	0.87 ± 0.09 ; 0.69	0.88 ± 0.09 ; 0.70	0.89 ± 0.14 ; 0.71	0.94 ± 0.08 ; 0.78	3.13 ± 2.00 ; 7.13	174.8 ± 52.4	82.5 ± 43.4	14.4 ± 20.1

hVOR: VOR gain in the plane of the horizontal SCC; VOR₄₀: Instantaneous gain at 40 ms; VOR₆₀: Instantaneous gain at 60 ms; VOR₈₀: Instantaneous gain at 80 ms; VOR_r: linear regression gain; VOR_p: position gain.

II. Topodiagnosis in Acute Vestibular Syndrome patients

1. Anticomensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus

The data from 43 consecutive patients aged 47 ± 18 years presenting with symptoms of spontaneous vertigo and SN (jerk nystagmus with horizontal component at gaze straight ahead) to the neurotology service (emergency room, elective consult) of a tertiary-care hospital in Lisbon were retrospectively analysed. The median time to evaluation after symptom onset was 2 days. According to clinical, caloric, ocular and cervical vestibular-evoked myogenic potential, cranial MRI results, and clinical follow-up (range 3-15 months) patients were diagnosed with peripheral (vestibular neuritis/labyrinthitis, $n=30$, definitive Ménière's disease⁶, $n=1$) and central (definitive or probable vestibular migraine⁷, $n=10$, stroke, $n=2$) disorders. Peripheral as well as migraine⁸ and stroke patients all had to fulfil the criterion of presenting with SN in order to enter the analysis. 23 of the peripheral patients were examined with vHIT at follow-up every 7-15 days in the first month and every 3-6 months after this. In addition, two other control groups were also studied: healthy subjects ($n=39$, age 39.9 ± 16.5 years), selected to match patients mean age and gender, and patients after acute vestibular neurectomy ($n=5$, age 55.7 ± 24.8 years) providing a positive control group.

SN horizontal slow phase velocity was similar between peripheral patient, central patient and positive control groups, ($p=0.187$; Grand Median= $4.30^\circ/s$). All peripheral patients and positive controls had AQEM with contralesional impulses (see **Figure 8A** for an example), 3 peripheral patients also with ipsilesional ones. Two healthy subjects showed AQEM, however, with an occurrence rate of only $0.3\% \pm 1.1\%$. Central patients did not have AQEM (see **Figure 8B** and **8C** for illustrative examples). AQEM occurrence rate was different between groups ($p<0.001$; **Figure 10A**), and was higher in peripheral patients with contralesional ($74 \pm 4\%$, mean \pm SD) in comparison to ipsilesional ($1 \pm 4\%$) impulses and also in comparison to healthy subjects ($p<0.001$, for all comparisons). AQEM occurrence rate was similar between peripheral patients

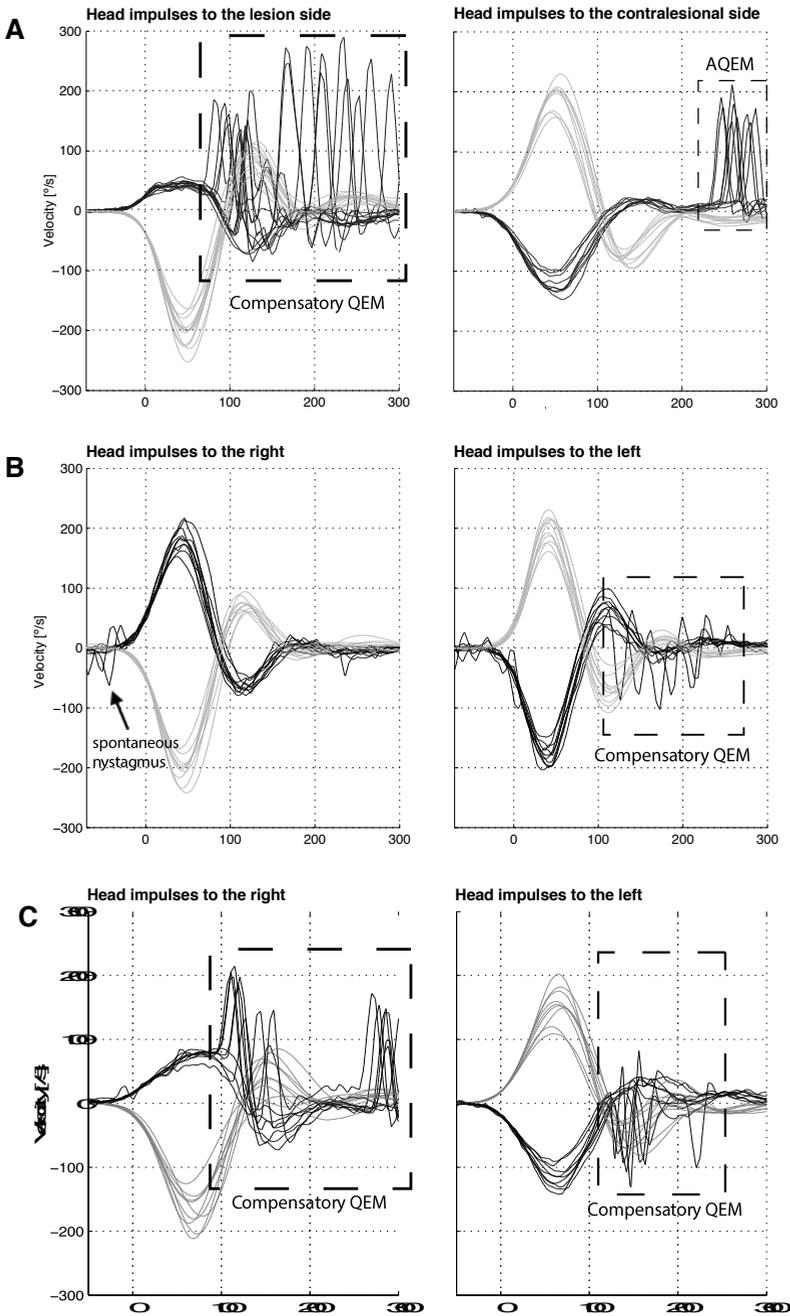
and positive controls with contralesional impulses ($66\pm 11\%$; $p=1.0$). AQEM latency was 231 ± 53 ms, amplitude $3.4\pm 1.4^\circ$ and peak velocity $166\pm 55^\circ/\text{s}$.

VOR gain in healthy subjects and central patients was similar with right and left impulses (Paired T-test $p>0.07$, all comparisons). VOR gain was lower with ipsilesional in comparison to contralesional impulses in both peripheral patient (0.32 ± 0.21 vs. 0.78 ± 0.18) and positive control (0.19 ± 0.17 vs. 0.68 ± 0.06) groups (Paired T-test $p<0.003$, all comparisons). VOR gain with ipsilesional impulses was similarly low in peripheral patient and positive control groups ($p=1.0$) and both significantly lower in comparison to healthy subject (0.86 ± 0.11) and central patient (0.87 ± 0.21) groups ($p<0.001$, all comparisons; **Figure 10B**).

At follow up, SN in darkness and AQEM were present in 10/23 of peripheral patients; in 2/23 head impulses triggered both nystagmus and AQEM.

The overall diagnostic accuracy for differentiating central from peripheral patients was 96% (95% CI for AUC ROC curve: 0.90 to 1.0) for VOR gain and 100% (95% CI for AUC ROC curve: 1.0 to 1.0) for AQEM occurrence rate.

Figure 8. AVL of peripheral or central etiology vHIT illustrative examples



AQEM – Anti-compensatory Quick Eye Movements, QEM – Quick Eye Movements.

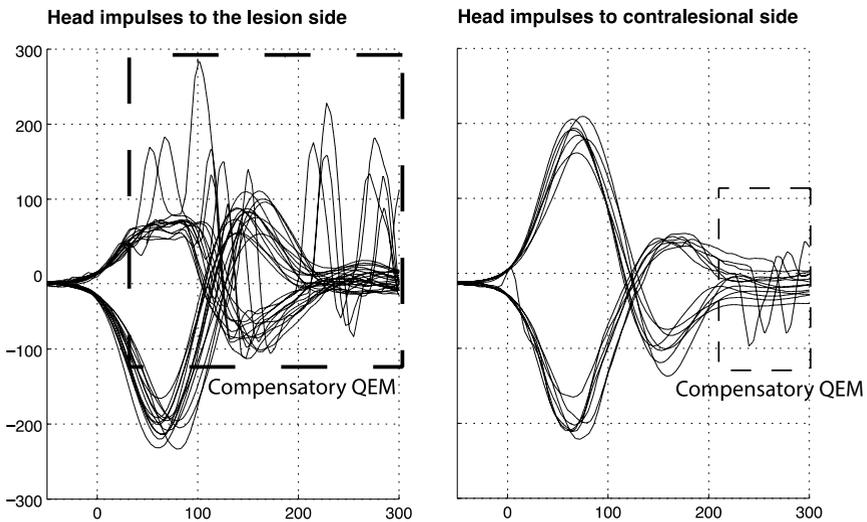
A. Anticomensatory quick eye movements (AQEM) with contralesional head impulses in a patient with vestibular neuritis. With head impulses to the lesion side the eyes

(black) do not compensate for the head (grey, each trace corresponds to one head impulse). The vestibulo-ocular reflex (VOR) is deficient (gain 0.25) and the patient makes compensatory refixation saccades. When the head is turned to the contralesional side (*), anticompensatory quick eye movements (AQEM), i.e. eye movements in the direction of the head movement can be observed (box). Low-velocity counter-impulses (**) are generated after head-impulse stop. The contralesional low VOR may result from a defective ipsilesional VOR inhibitory pathway.

B. Normal head impulses to the right and left (gain 0.88 and 0.90, respectively) in a patient with central aetiology of right spontaneous nystagmus (migrainous vertigo). No AQEM can be observed with head impulses.

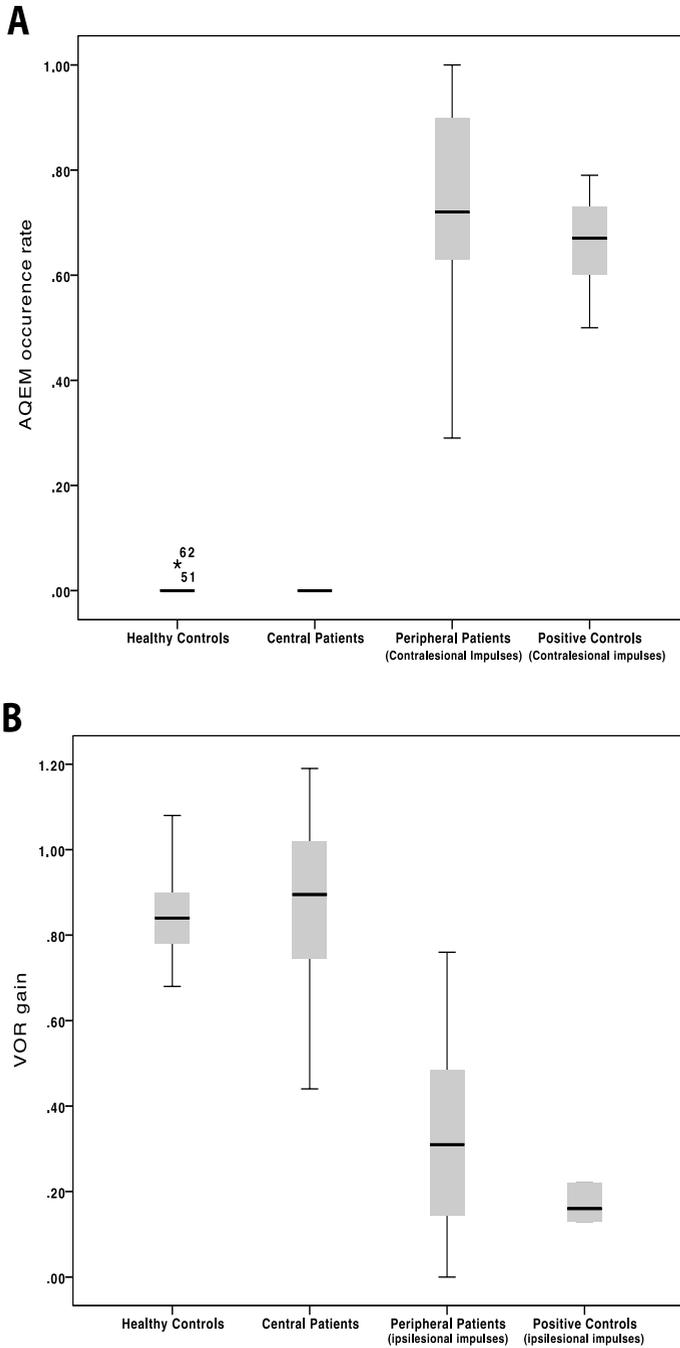
C. Pathological head impulses to the right and left (gain 0.43 and 0.56, respectively) in a patient with central aetiology of right spontaneous nystagmus (Anterior inferior cerebellar artery stroke, T1 hypointense and T2/flair hyperintense acute ischemic lesion in the right middle cerebellar peduncle). No AQEM can be observed with head impulses.

Figure 9. Chronic unilateral vestibular lesion after unilateral vestibular neuritis with no spontaneous nystagmus.



With head impulses to the lesion side the eyes do not compensate for the head. The vestibulo-ocular reflex (VOR) is deficient and the patient makes covert and overt compensatory refixation saccades. When the head is turned to the contralesional side small amplitude compensatory refixation saccades are triggered but no anticompensatory quick eye movements (AQEM). Note that low-velocity counter-impulses are generated after head-impulse stop.

Figure 10. AQEM occurrence rate and VOR gain in central and peripheral patients and healthy and positive controls.



Boxplot whiskers indicate the range of the data, the box middle line the median value, and the box edges the upper and lower quartile.

- A.** *Anti-compensatory quick eye movements (AQEM) occurrence.* Boxplots show AQEM occurrence rate for healthy controls (n=39), central patients (n=12), peripheral patients (n=31) and positive controls (neurectomy patients; n=5), the two later during contralesional impulses. AQEM occurrence rate was higher in peripheral patients with contralesional impulses in comparison to central patients and healthy subjects ($p < 0.001$, for all comparisons) but similar to positive controls ($p = 1.0$).
- B.** *VOR gain.* Boxplots show VOR gain for healthy controls, central patients, peripheral patients and positive controls, the two later during ipsilesional impulses. VOR gain with ipsilesional impulses was similarly low in peripheral patients and positive control groups ($p = 1.0$) and both significantly lower in comparison to healthy subject and central patient groups ($p < 0.001$, all comparisons).

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2. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials

Case Report

A 42-year-old man was admitted to the emergency room with acute spontaneous and spinning vertigo with nausea and vomiting. He had no cochlear symptoms, history of trauma or prior complaints of vertigo, dizziness, vestibular, visual or postural symptoms. Examination revealed a grade III left horizontal SN.

During positional testing, the intensity, but not the direction, of the nystagmus changed (almost stopping with the head pitched down about 30° and decreasing during leaning, in the left Pagnini-McClure and left Dix-Hallpike maneuvers). During the Pagnini-McClure maneuver nystagmus was apogeotropic on the right and geotropic (and weaker) on the left.

The neurological examination was otherwise unremarkable, as was the clinical head-impulse test (HIT). Brain MRI was normal. Since assessment of the pathophysiology and identification of the affected side were not possible clinically, vHIT and VEMPs were performed.

A video-oculography device (EyeSeeCam®) was used to perform the vHIT. Three trials (20 head impulses each) were passively and randomly applied towards either side in the plane of the horizontal SCC, to check for reproducibility. VOR gain was significantly reduced in head impulses to the right, but normal to the left (head velocities from 200 to 300°/s). From 40 to 90 ms after head movement initiation the eye velocity saturated and remained constant at 80 °/s, yielding a median gain of 0.29 at 60 ms (**Figure 11 day 1**). Left overt compensatory saccades were triggered during right impulses (120-260 ms latency). Anti-compensatory quick phases were triggered by left impulses and locked at 260-320 ms. cVEMPs and oVEMPs were absent after right-side stimulation (**Figure 12 day 1**).

With only the results of the clinical examination, this patient would most probably have been diagnosed to have right vestibular neuritis and treated accordingly. It was, in particular, the remarkable saturation of eye velocities during head impulses to the right that led us to hypothesize an otoconia plug in the right horizontal canal. To the best of our knowledge, such a peculiar eye

velocity trajectory has never been described in the literature before, for example as a characteristic for vestibular neuritis or any other known condition. On the basis of this high-frequency VOR deficit and the gravity-dependent SN, as well as the observation that the Pagnini-McClure maneuver did not cause geotropic nystagmus on both sides, the alternative hypothesis of a right horizontal canalolithiasis was also rejected.

The examining first author therefore decided to perform a liberatory maneuver by positioning the patient from sitting to lying on the right side and then turning his head quickly down 45° (Migueis et al. 2005). In contrast to a Gufoni maneuver, which would have generated an endolymph ampulofugal movement, this maneuver utilized the increased inertia of the hypothesized otoconial canal plug. When the patient returned to a sitting position, a right-beating horizontal nystagmus appeared (Video 6). A subsequent Pagnini-McClure maneuver test indicated that the debris had been mobilized in the canal, because the nystagmus was now geotropic on both right and left. Then a 360° body rotation around the longitudinal axis to the left was performed (8). This evoked a left-beating nystagmus during the first 180-270° rotation, suggesting that the debris moved along the long arm of the right horizontal SCC back into the utricular cavity. The patient was free of symptoms and SN when released from the emergency unit.

Forty-eight hours later, he was still symptom-free and clinical examination was unremarkable. The eye velocity profile during right vHIT was now normally shaped, with no cut-off, but there was still a slightly lower VOR gain on the right than on the left side (0.81 vs. 1.09). Compensatory saccades were no longer triggered. Surprisingly, cVEMPs and oVEMPs were still absent, although the patient was now symptom-free.

Thirty days later, clinical examination was completely normal. VHT results were normal without VOR gain asymmetry between the sides. CVEMPs and oVEMPs had normal bilateral trajectory and latency values, although a slight interaural amplitude difference (IA) was still present. This completely recovered by day 80.

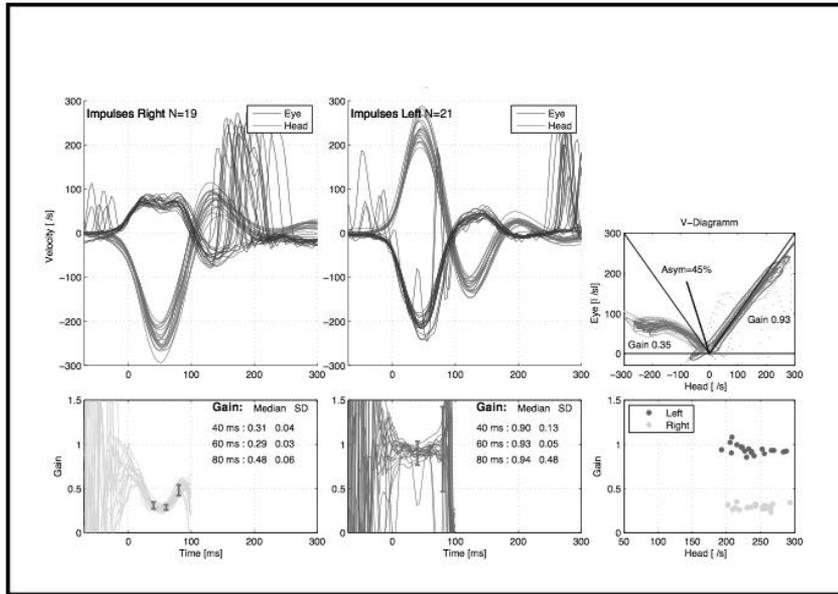
Eight months after the first event, the patient was readmitted to emergency department after 48 hours of positional vertigo. A right geotropic hBPPV was diagnosed. He was again successfully treated with a 360° body

rotation around the longitudinal axis to the left. Before, as well as after this rehabilitation maneuver, a mild asymmetry between sides was recorded both with vHIT (0,81 vs. 1,04) and cVEMP testing (IA=0.30) (**Figure 13**). oVEMP testing was normal. At day 30, clinical examination, vHIT and VEMP testing were all normal.

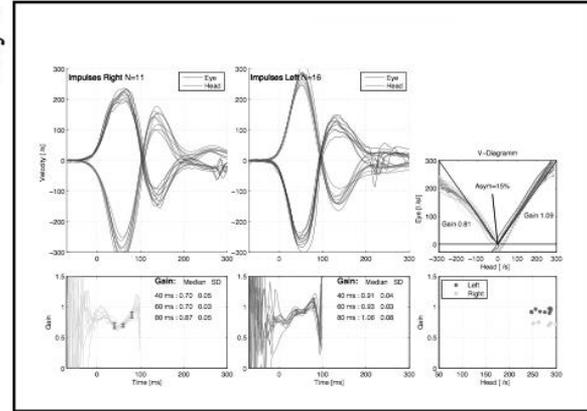
Since day 30 after the first event, right cVEMP latencies were persistently slightly increased (p13/n23 average of 6 recordings: 15.9/24.3 ms on the right side and 15.2/23.3 ms on the left side; $p < 0.05$, paired T Test) but not oVEMP latencies.

Figure 11. Video head-impulse test (vHIT) recordings.

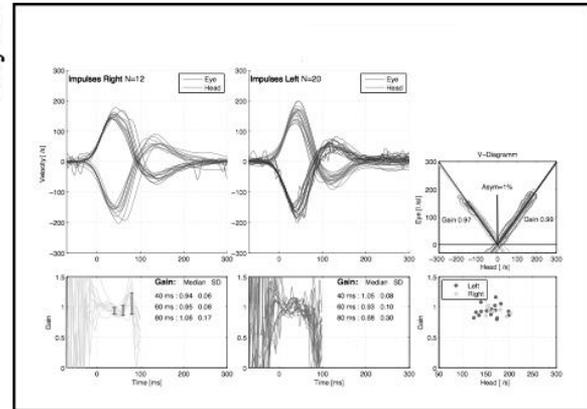
Day 1



Day 3



Day 30



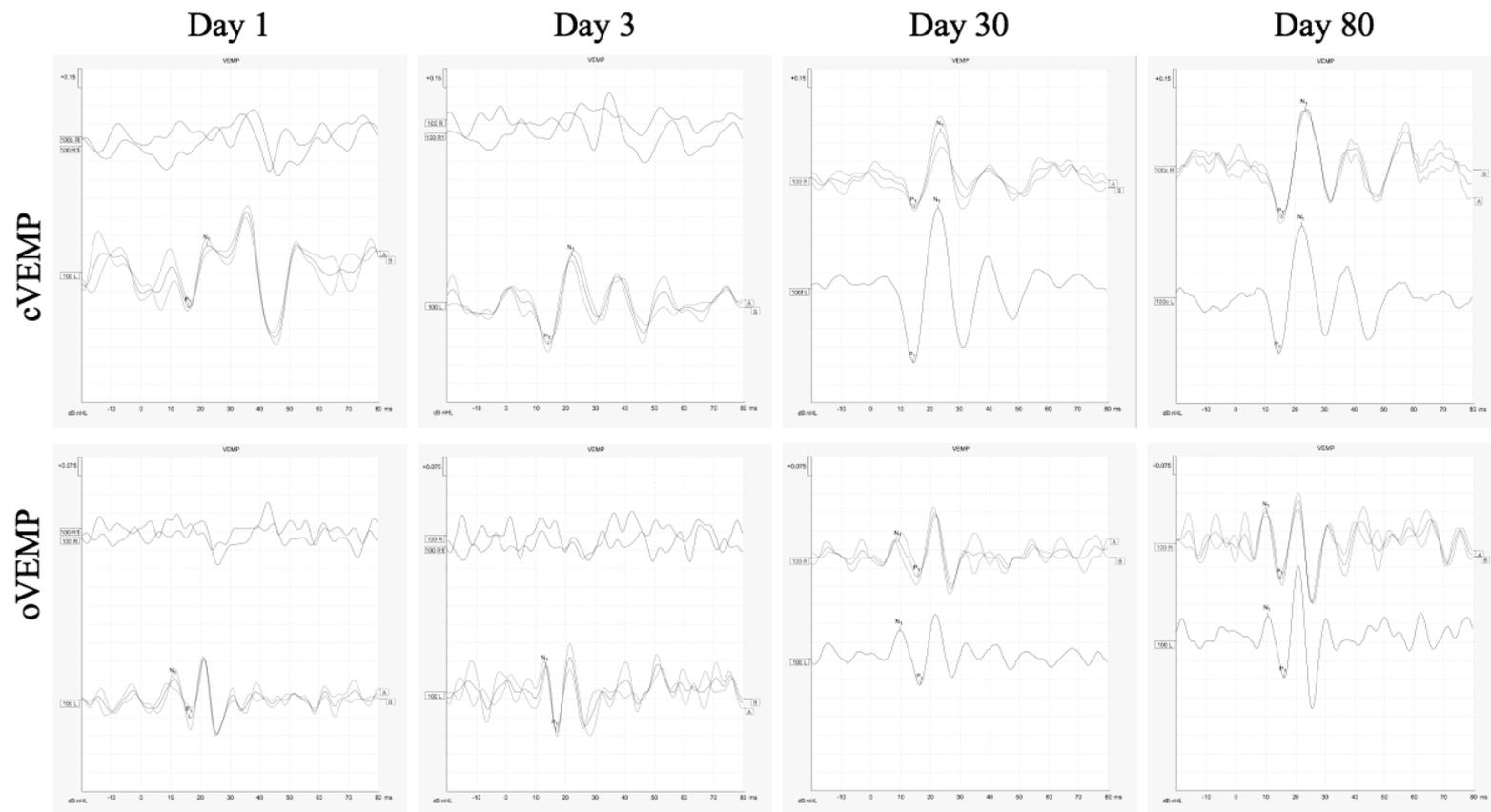
In each trial and for all valid head impulses, the two left upper plots show the velocity trajectories ($^{\circ}/s$) of the eye (black) and head (grey) and the right upper plot the regressions of eye and head velocity during right (light grey) and left (dark grey) impulses; the two left lower plots show the time course (ms) of the VOR gain (eye velocity/ head velocity) and the right lower plot the VOR gain values at 60 ms.

vHIT on day 1. During right HIT, note the saturated profile of the eye velocity curve and the low VOR gain (0.31, 0.29 and 0.48 at 40, 60 and 80 ms, respectively), as well as the corrective saccades triggered from 120 to 260 ms. Note also the saccades during left HIT, randomly present in the first 100 ms but also later locked at around 300 ms (corresponding to the fast phase of the spontaneous nystagmus). For rightward head impulses the eye velocity saturated and remained constant at $80^{\circ}/s$ with head velocities above $150^{\circ}/s$. This saturation can also be observed in the regression diagram and in the eye and head velocity trajectories.

vHIT on day 3. The eye velocity curve regained its normal trajectory although the VOR gain still shows a slight asymmetry.

vHIT on day 30. The eye velocity curve has a completely normal trajectory, and the VOR gain is symmetrical. No saccades were triggered.

Figure 12. cVEMP and oVEMP recordings on days 1, 3, 30 and 80.



An Eclipse® vestibular EP from Interacoustics® was used for recordings. The vestibulocollic and vestibulo-ocular reflexes were evoked by rarefaction and a 500 Hz tone burst (5.1 Hz stimulation rate, 100 dB nHL) delivered unilaterally to the homolateral (cVEMPs) and contralateral (oVEMPs) ear by a pair of insert earphones. A total of 200 and 500 recordings, respectively and separately, were averaged. Scaling of cVEMP and oVEMP amplitudes was applied according to muscle tonus level just before and immediately after each stimulus during the entire test. “A” curve holding all rarefaction sweeps and “B” curve holding all condensation sweeps were recorded independently and are shown for reproducibility.

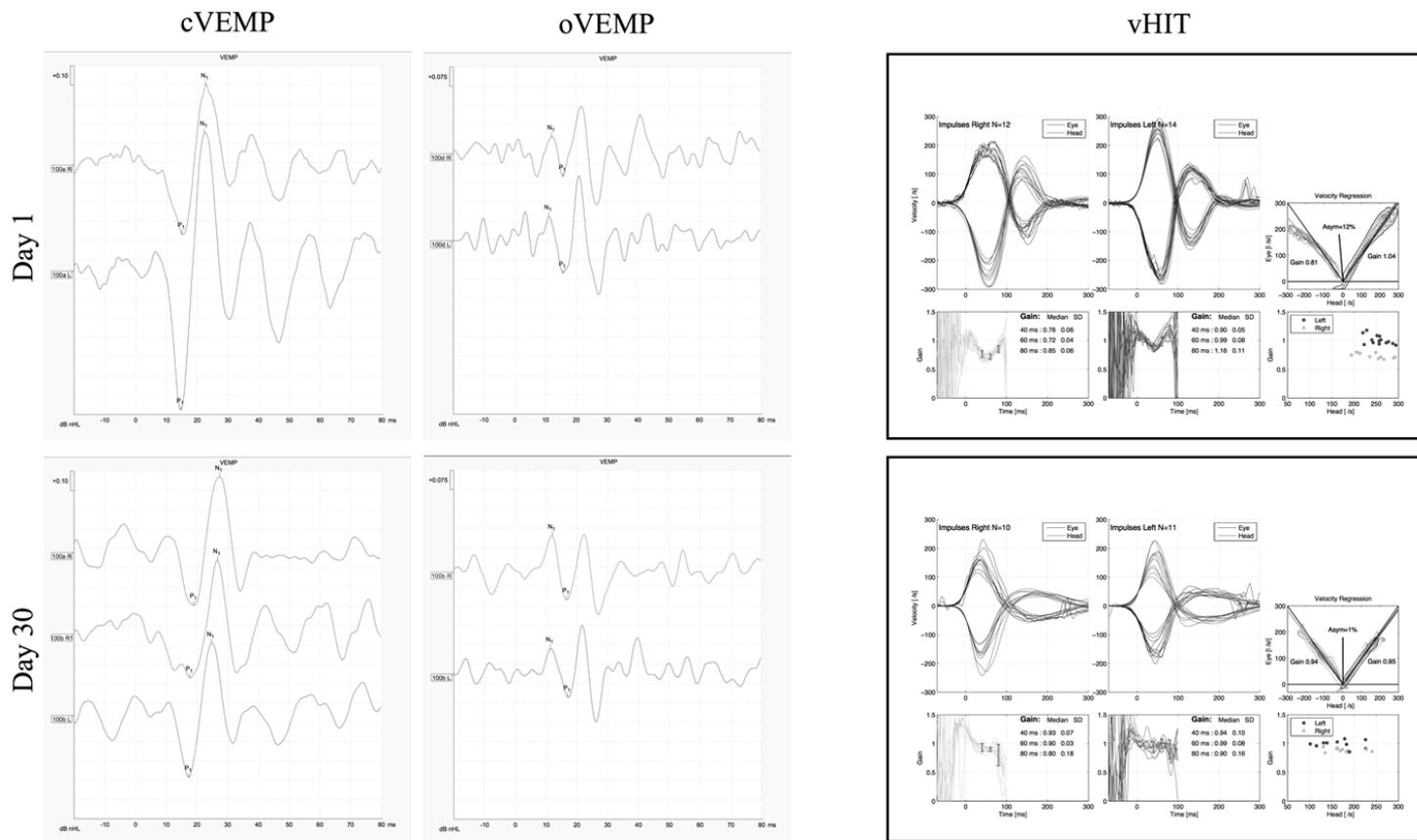
Day 1. Note that Right (R) cVEMPs and oVEMPs are absent and that Left (L) cVEMPs and oVEMPs are normal.

Day 3. Right (R) cVEMP and oVEMP are still absent and Left (L) cVEMP and oVEMP are normal.

Day 30. Right cVEMPs have normal morphology and latency. The interaural amplitude (IA) difference with scaled curves (IA=0.34) is already below the upper normal limit (IA<0.35). OVEMP responses are symmetrical (IA=0.21).

Day 80. CVEMPs and oVEMPs are symmetrical with IA of 0.08 and 0.05, respectively.

Figure 13. Video head-impulse test (vHIT), cVEMP and oVEMP recordings during the second hBPPV event (right geotropic hBPPV), 8 months after the first event.



Day 1. *vHIT*: although both eye velocity curves show normal trajectories, there is a lower VOR gain to the right (0.76, 0.72 and 0.85 to the right and 0.90, 0.99 and 1.16 at 40, 60 and 80 ms, respectively) with an asymmetry of 12% between sides in the regression velocity diagram. *VEMPs*: There's a cVEMP light asymmetry between sides (IA= 0.30) but within normal limits; oVEMPs are normal (IA=0,17)

Day 30. *vHIT*: The eye velocity curve regained its normal symmetry, both dynamically from 40 to 80 ms and from regression data (asymmetry of 1%). *VEMPs*: cVEMPs and oVEMPs are symmetrical with IA of 0.03 and 0.14, respectively.

III. Topodiagnosis in non-acute vestibular lesions

1. Inferior peduncle lesion presenting with bilaterally impaired vestibular responses to horizontal and posterior head impulses

Case Report

A 36-year old man presented with a one-year history of progressive unsteadiness, particularly when in darkness. He had no cochlear symptoms, history of trauma or prior complaints of vertigo, dizziness, or vestibular, visual or postural symptoms.

An examination revealed no spontaneous, gaze-evoked or positional nystagmus. The clinical head-impulse test (HIT) was pathologic bilaterally when testing the horizontal canals and normal when testing the vertical canals. The neurological examination was otherwise unremarkable.

The video-Head Impulse Test (vHIT)¹ (**Figure 14b**) revealed a significantly reduced vestibulo-ocular reflex (VOR) gain in both horizontal (0.38 ± 0.07 and 0.29 ± 0.05) and posterior canals (0.49 ± 0.05 and 0.38 ± 0.06) with covert and overt corrective saccades, but normal VOR responses in both anterior canals (0.89 ± 0.08 and 1.04 ± 0.15), for right and left impulses, respectively.

With caloric testing, there was a right unilateral weakness (56%). The remaining oculomotor tests were normal. oVEMP and cVEMP responses were normal and symmetrical. A brain MRI (**Figure 14a**) disclosed a left inferior cerebellar peduncle lesion suggestive of a glioma.

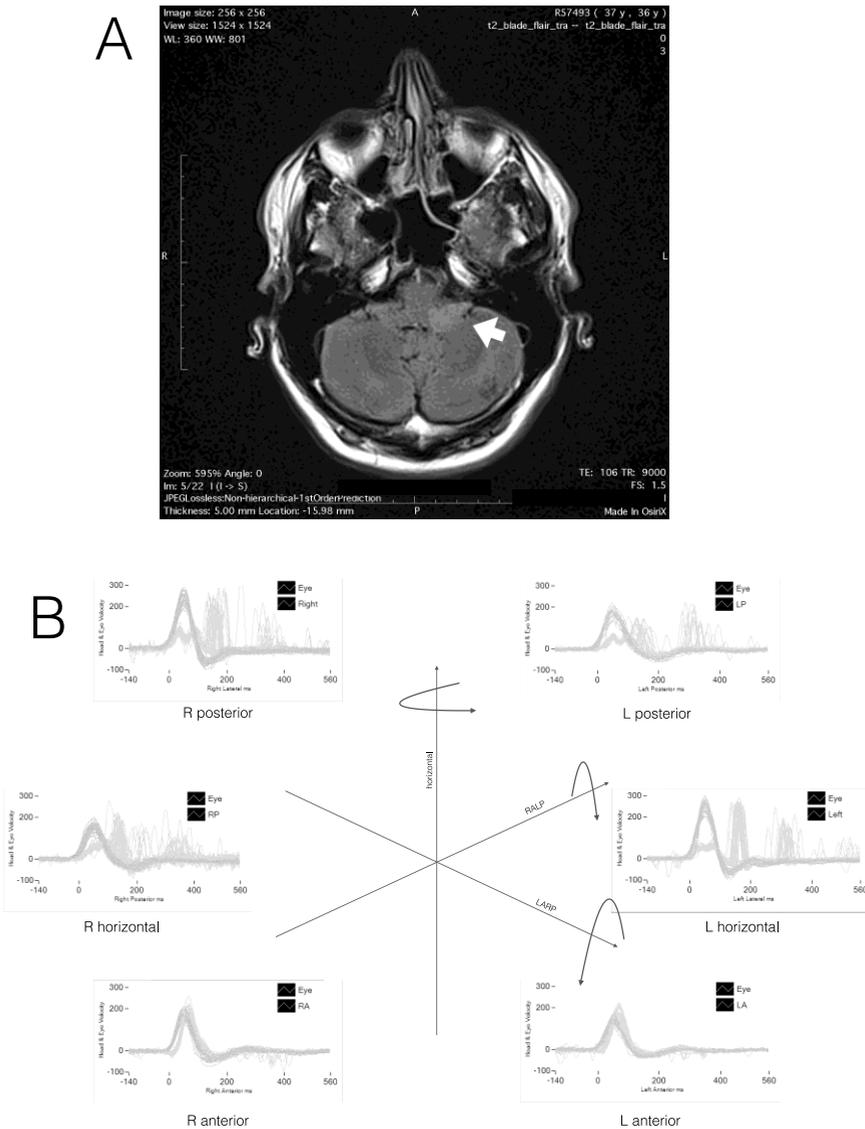


Figure 14. Brain MRI with contrast, 3D vHIT and VEMP.

- A. Left inferior peduncle lesion on axial T2-image.
 B. Video Head Impulse. The plots show the velocity trajectories (o/s) of the eye and head for LARP (left anterior-right posterior), RALP (right anterior-left posterior) and lateral semicircular canal stimulation (cont.) with about 20 brief, unpredictable head turns in the direction of each semicircular canal. Each trace corresponds to one head impulse. With head impulses in the direction of both horizontal and posterior

semicircular canals, the eyes (green) do not compensate for the head (blue for left, red for right). The VOR is deficient and the patient makes compensatory refixation saccades during, and after, the head impulses. With head impulses in the direction of both anterior semicircular canals, the eyes compensate for the head.

IV. vHIT topodiagnostic in hereditary neurodegenerative disorders with and without involvement of central vestibular pathways.

1. Vestibulo-ocular reflex dynamics with head-impulses in Huntington's disease

We explored 18 genetically confirmed HD patients (44.7 ± 8.1 years; male=9), classified as Shoulson and Fahn severity stages 1(n=5; pre-symptomatic), 2(n=4), 3(n=8) and 4(n=1) based on their Total Functional Capacity (TFC) scores, and 40 healthy controls (39.9 ± 16.5 years; male=20).

VOR latency and VOR gain were not different from controls (**Table 8**; $p > 0.29$ for both comparisons). No differences were found between presymptomatic and symptomatic patients. QEM were present in 11 patients and 18 controls, always after the head impulse and compensatory (overt saccades). QEM latency (174.5 ± 41.2 ms), peak velocity (71.58 ± 34.48 °/s) and occurrence rate (0.45 ± 0.29) were not different from controls ($p > 0.11$ for all comparisons). Though not realizing it, 5 of the symptomatic patients majorly failed to direct gaze in darkness, both horizontal as vertically, this correlating with TFC scores (Spearman $r = 0.65$, $p = 0.005$).

Table 8. VOR gain and QEM results in Huntington's patients

Population size	hVOR					Saccades		
	VOR ₄₀	VOR ₆₀	VOR ₈₀	VOR _r	Asymmetry (ms)	latency	peak-velocity	occurrence
n=18	0.86 ± 0.11	0.82 ± 0.11	0.96 ± 0.10	0.96 ± 0.07	4.56 ± 2.90	174.5 ± 41.2	71.58 ± 34.4	0.45 ± 0.29

hVOR: VOR gain in the plane of the horizontal SCC; VOR₄₀: Instantaneous gain at 40 ms; VOR₆₀: Instantaneous gain at 60 ms; VOR₈₀: Instantaneous gain at 80 ms; VOR_r: linear regression gain; VOR_p: position gain.

2. Vestibulo-ocular reflex dynamics with head-impulses in hereditary cerebellar ataxias

We studied 23 patients with a clinical and genetically confirmed diagnosis of spinocerebellar ataxia (SCA) type 3 (n=15), type 2 (n=4) and type 1 (n=4)], and 9 patients with early onset Friedreich's ataxia (FA) (**Table 9**). A group of 40 age- and gender-matched healthy subjects without previous history of cochlear, vestibular or visual diseases, and not taking medication that may potentially affect eye movement, were used as controls.

Disease severity was evaluated with the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübisch et al. 2006), applied independently by two neurologists. All subjects provided their informed written consent to the study protocol, which was approved by the Ethics Committee.

Table 9. Hereditary ataxia patients' and controls' characteristics

	FA (n=9)	SCA3 (n=15)	SCA1 (n=4)	SCA2 (n=4)	Controls (n=40)	P
Female (%)	44.4	53.3	50.0	25.0	55.0	$\chi^2=1.52$; $p=0.82$
Age‡	36.3±12.0	49.8±11.9	48.5±16.5	46.5±14.9	41.10±16.6	0.10
Disease duration‡	23.3±15.7	6.8 ±4.1	8.3±4.6	15.3±3.6	NA	0.001
SARA	22.6±7.7	13.9±6.1	12.1±3.4	12.9±6.6	NA	0.02

FA: Friedreich's ataxia; SCA: Spinocerebellar ataxia; SARA: Scale for the Assessment and Rating of Ataxia; NA – not applicable;

‡ age and disease duration are expressed in years ± standard deviation.

VOR slow phase

Figure 15 shows vHIT illustrator examples for FA, SCA3 and controls. **Table 10** and **Figure 16** show the main results for the VOR slow phase.

VOR latency was longer in SCA3 and FA, as compared to controls ($p \leq 0.022$ and $p \leq 0.001$, respectively). VOR latency AUC-ROC was 0.88 (95% CI, 0.76 to 1.00) for FA. For a threshold of 13.2 ms, the sensitivity was 100.0% and the specificity 82.6%. VOR_r , VOR_{40} and VOR_{60} were lower in SCA3 and FA, as compared to controls ($p \leq 0.006$ for all comparisons) with a high proportion of FA (100%), SCA3 (80%) and SCA1 (75%) patients having an unilateral or bilateral abnormally low VOR_r (below 0.77, defined as mean VOR_r minus 2SD found in control group). VOR_{80} was only lower in SCA3, as compared to controls ($p \leq 0.004$). VOR_r gain showed a significant negative correlation with disease severity evaluated with SARA (Spearman $r = -0.46$, $p = 0.01$). VOR_{80} AUC-ROC was 0.78 (95% CI, 0.61 to 0.95) for SCA3. For a threshold of 0.66, the sensitivity was 73.3% and the specificity 77.0%. VOR_{80} and ($VOR_{80} - VOR_{40}$) did not correlate with latency.

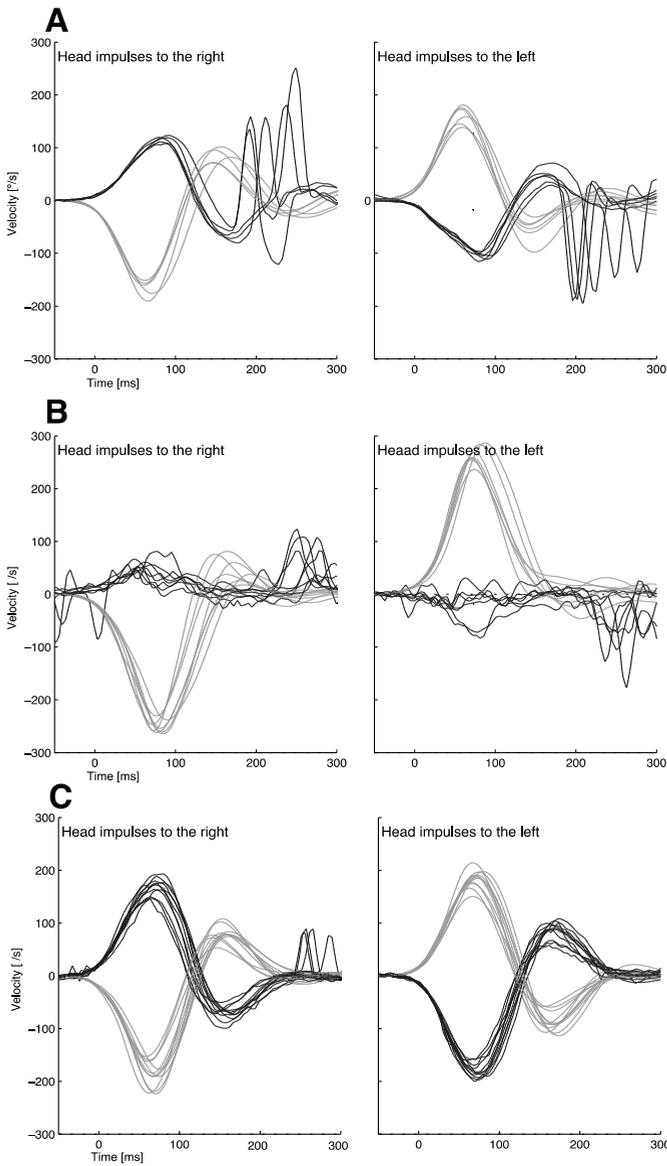
Table 10. VOR slow phase results.

	FA (n=9)	SCA 3 (n=15)	SCA 1 (n=4)	SCA 2 (n=4)	Control (n=40)	P value‡‡
VOR latency (ms)	23.7±15.7	7.8±15.0	3.6±3.1	-1.4±2.3	-2.3±2.1	<0.001
VOR_r	0.42±0.17	0.50±0.30	0.77±0.05	1.00±0.06	0.94±0.08	<0.001
Abnormal‡(%)	100	87	75	0	0	χ²=61.0; p<0.001
VOR asymmetry	3.00±2.60	4.73±3.63	3.75±2.87	3.50±1.92	3.13±2.00	0.701
VOR gain dynamics						
VOR ₄₀	0.39±0.13	0.43±0.32	0.75±0.12	0.95±0.13	0.87±0.09	<0.001
VOR ₆₀	0.42±0.19	0.41±0.34	0.83±0.25	0.95±0.12	0.88±0.09	<0.001
VOR ₈₀	0.62±0.28	0.46±0.35	1.02±0.31	0.99±0.04	0.89±0.14	<0.001

Results for VOR gain, is expressed as mean ± standard deviation. FA: Friedreich's ataxia; SCA: Spinocerebellar ataxia; NA – not applicable.

‡ Abnormal VOR gain defined as VOR_r gain below the mean minus 2SD of control values (0.78).

‡‡ Pearson's Chi-Square test and independent samples Kruskal-Wallis test results for categorical and continuous data, respectively.

Figure 15. vHIT illustrative examples.

A: vHIT of a patient diagnosed with Friedreich's ataxia; with head impulses towards either side the eyes (black) do not compensate for the head (grey, each trace corresponds to one head impulse) and catch-up saccades are triggered after the head impulse (overt saccades). B: vHIT of a patient diagnosed with SCA3: note the significant defective VOR slow phase during impulses to both sides and catch-up saccades triggered after the head impulse. C: vHIT of a control subject: note the compensatory VOR slow phase during impulses to both sides; low occurrence rate and low peak velocity catch-up saccades are triggered after right head impulses.

Table 11. Catch-up saccades

	FA (n=9)	SCA 3 (n=15)	SCA 1 (n=4)	SCA 2 (n=4)	Control (n=40)	P value‡
Covert saccades						
subjects with (%)	0	20	0	0	0	$\chi^2=14.4$; $p=0.006$
occurrence rate (%)	0	11.1±28.5	0	0	0	0.02
latency (ms)	NA	113.2±15.1	NA	NA	NA	NA
peak velocity (°/s)	NA	77.50±15.30	NA	NA	NA	NA
Overt saccades						
subjects with (%)	88.9	86.7	75.0	100	50.0	$\chi^2=11.8$; $p=0.02$
occurrence rate (%)	46.1±42.9	56.5±36.5	19.8±26.1	23.3±15.4	14.4±20.1	0.001
latency (ms)	223.5±37.5	194.0±38.5	190.0±33.5	211.9±22.7	174.8±52.4	0.18
peak velocity (°/s)	226.4±52.5	150.7±72.9	101.5±48.98	68.9±22.9	82.5±43.4	<0.001

Results for QEM occurrence rate, latency and peak velocity are expressed as mean \pm standard deviation. FA: Friedreich's ataxia; SCA: Spinocerebellar ataxia; NA – not applicable.

‡ Pearson's Chi-Square test and independent samples Kruskal-Wallis test results for categorical and continuous data, respectively.

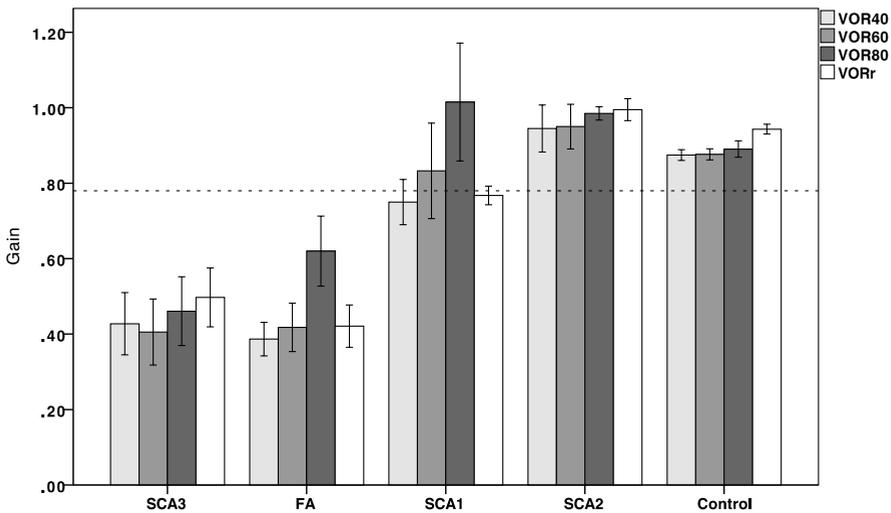
Catch-up saccades

Table 11 shows the main characteristics of catch-up saccades triggered with head impulses.

Covert saccades were only present in three SCA3 patients and with a low occurrence rate ($11.1 \pm 28.5\%$). Overt saccades (triggered after the head impulse) were present in all groups, with an occurrence rate only significantly higher in SCA3 patients than in controls ($p < 0.001$).

Overt saccades occurrence rate and peak-velocity showed a significant negative correlation with VOR_{40} (Spearman $r = -0.32$ and $r = -0.63$, respectively, $p = 0.01$).

Figure 16. VOR gain dynamics



Bar graph showing VOR_r , VOR_{40} , VOR_{60} and VOR_{80} average results for SCA3, FA, SCA1, SCA2 and controls. VOR_r , VOR_{40} and VOR_{60} were significantly lower in FA and SCA3 in comparison to SCA2 and controls ($p \leq 0.006$ for all comparisons) but regarding VOR_{80} only SCA3 was different from SCA2 and controls ($p \leq 0.004$ for all comparisons). The instantaneous gain difference from 40 to 80 ms was higher in FA in comparison to controls ($p = 0.01$). The dotted line represents VOR_r normal lower limit (0.77) as calculated by (average-2SD) for controls. Error bars represent standard error of mean.

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CHAPTER V

**GENERAL DISCUSSION AND
CONCLUDING REMARKS**

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General Discussion

High frequency evaluation of VOR responses with head impulses is now a well-established evaluation modality strictly correlated and closely comparable to the gold standard scleral search coils, both in normal subjects and in central and peripheral patients, with the advantages of being non-invasive and easier to use in the clinical setting. The research carried out and reported here has taken these advantages as an opportunity to carry out neurophysiological studies on the oculomotor responses generated by head impulses in humans. In this study, we explored the differential consequences that peripheral vestibular and central nervous system lesions known to have VOR dysfunctions might have on VOR control, covert and overt saccades generation, and even on the vestibular evoked myogenic potentials (VEMPs). Our aim was to determine the clinical utility of the test and to increase our knowledge on the mechanisms responsible for eye movement control during HIT.

In the next pages, a general discussion is done about the results presented in Chapter IV, following the same order.

I. vHIT evaluation in normal subjects

1. Normal Vestibulo-ocular Reflex Gain and Quick Eye Movements with Horizontal Head Impulses

The gold standard for calculating the VOR gain was introduced by Aw et al (1996). The method is based on the ratio of eye to head velocity at instantaneous points in time. A good compensatory VOR is equivalent to a ratio close to unity. When plotted over time, the resulting time course of the VOR gain approximately assumes a linear trajectory that resembles a line at a constant ordinate value of 1.0. Such characteristic horizontal lines have been documented in search coil examinations, e.g., by Glasauer et al (2004) and Bzezny et al (2003). For VOR deficits, deviations from the line of unity can be observed (e.g. Kremmyda et al 2012 and Glasauer et al 2004).

In the absence of camera slippage (**Figure 17**), a constant linear trajectory close to unity is also present in the time course of the vHIT gain of healthy control subjects (**Figure 3B**). In the initial phase of the head movement, however, camera slippage might affect the gain trajectory by adding slippage velocity as an artefact to the eye velocity traces. In contrast, the head movement traces will remain largely unaffected due to the differences in eye and head radii.

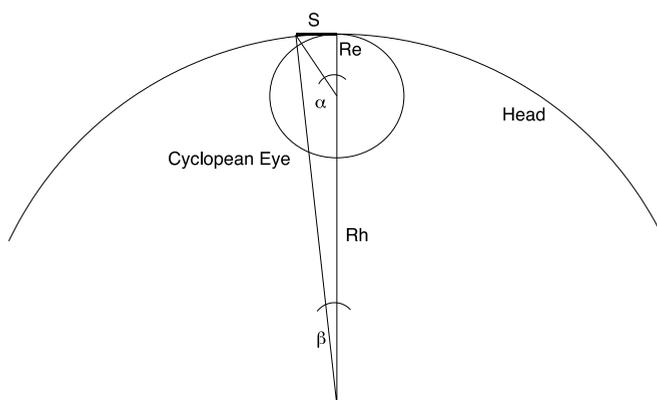


Figure 17. : Geometrical setup of a VOG device measuring a cyclopean eye with radius R_e . The head radius is R_h . A small camera slippage S is mistaken for a small head rotation β , but for a large eye rotation α .

If applied by a human examiner, the distribution of eye velocity traces can be far from normal. In contrast, the instantaneous. Therefore, the time course of the VOR gain provides sensitive information about camera slippage, even in clinical settings, where a search coil allowing a comparison with the gold standard is unavailable. If the vHIT system plots the gain traces in real time during the application of head impulses, the examiner can immediately assess data quality, which is mainly determined by the slippage content. Such a feedback is particularly useful for training. During a mandatory training phase, examiners should therefore first try to improve their skills on healthy volunteers until they are sure that they can generate the largely linear gain trajectories, which are to be expected from normal vestibular functions [(Luis et al. Human vestibulo-ocular reflex dynamics examined through the video Head Impulse Test. *Clin Neurophysiol* 2015 (in print)].

As long as “bump artefacts” extending beyond the point of instantaneous gain calculation are observed, examiners should consider eliminating the possible causes of artefacts outlined by Mantokoudis et al (2015). Possible causes are, in particular, goggle instability on the subject’s nose (Versino et al 2014), loose straps, touching goggles, and moving the soft tissue beneath the goggles. A workaround is to stabilize the goggle on the subject’s nose either by using a personalized cast made of dental impression paste (Versino et al 2014) or by taping the nose with a few layers of adhesive bandage. The other listed causes like wrong calibration, blinks, patient inattention, and pupil tracking loss do not yield systematic “bump artefacts” and can therefore be avoided more easily, for example, by repeating vHIT and calibration trials. In any case, examiners in their training phase can monitor the success of the countermeasures by observing the time course of the gain in healthy subjects and comparing them with the normal gain trajectory, which is expected to be constant and close to unity. In our study $VOR_{40}=0.87\pm 0.09$, $VOR_{60}=0.88\pm 0.09$ and $VOR_{80}=0.89\pm 0.14$, reflecting, in average, the above described linear gain trajectory expected to be found in healthy subjects.

In addition we estimated the VOR with a new calculation method, the linear regression gain (Luis et al. 2013). This calculation method yields a function of eye velocity to head velocity, showing a linear, constant gain of about one ($VOR_R=0.94\pm 0.08$).

We have finally demonstrated that quick-eye movements with head impulses may be found in a normal population, though only after and not during the head impulses and with a rather low peak-velocity and occurrence rate.

II. vHIT topodiagnosis in Acute Vestibular Syndrome patients

1. Anticomensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus

AQEM seem to be a useful sign to differentiate central from peripheral pathologies in patients with spontaneous nystagmus. They could be particularly important in central pathologies affecting VOR gain (see **Figure 8C**), as in anterior inferior cerebellar artery strokes (Newman-Toker et al. 2013).

We suggest that AQEM may be a sign of vestibular imbalance in a peripheral deficit. Contralesional impulses cause a short high-amplitude increase in the level of persisting vestibular imbalance (Schneider et al. 2004) driving the eyes instantaneously faster and further towards the lesion. When the eye reaches an eccentric position in the orbit, a quick phase is generated to reset gaze. This quick phase is recorded in the vHIT as AQEM. This hypothesis is supported by the observation that AQEM can be triggered in patients with SN and in patients in whom head movements trigger SN, in the latter even after 15 months after onset. In short, AQEM unmask vestibular tone imbalances, similarly to blinks. (Schneider et al. 2004) In central patients, SN is not of vestibular origin, and, therefore, head impulses do not trigger AQEM.

An alternative hypothesis where AQEM are compensatory QEM for counter-impulses (Fig 1A) is unlikely as they are neither present in central patients with similar VOR lesions and counter-impulses (Fig 1C) nor in peripheral patients no longer presenting SN (**Figure 9**). Also, a significantly higher VOR gain does not seem to justify why AQEM were absent in the central disorder group, as they were also absent in central disorder patients with unilateral or bilateral low VOR gain (see Fig. 1C for one example).

This retrospective work presents a number of limitations, as patients were not systematically evaluated with the same complementary studies, namely the gold-standard magnetic resonance imaging, or *quantitatively* evaluated with the HINTS protocol.² Also, only two stroke patients fulfilled the inclusion criteria. After these limitations are addressed in a future cohort study, AQEM should be added to the evaluation of the video head impulse test in addition to VOR gain and refixation saccades.

2. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials

This case is special in four respects: 1) the properties of the spontaneous nystagmus, which depended on head orientation with respect to gravity, indicating that a plug of otoconia debris blocked the right SCC; 2) the reversibility of a high horizontal VOR function asymmetry documented in the vHIT, early after liberatory maneuvers; 3) the high asymmetry of both cVEMPs and oVEMPs before and 2 days after the liberatory maneuvers; 4) VEMP recovery 30 days after treatment.

Clinical course of horizontal semicircular canal plugging.

VHIT was used for the first time to document a high-frequency VOR hypofunction during BPPV that improved within 2 days after treatment and returned to normal within 30 days. Of particular interest was a remarkable eye velocity trajectory that saturated at about $80^\circ/\text{s}$ as if the cupula was kept at a constant deflection, regardless of head velocity increases up to $300^\circ/\text{s}$. Reversible low-frequency VOR hypofunction has been previously reported in hBPPV canalolithiasis using calorics (Strupp et al., 1995).

The most plausible explanation for both the saturation of the eye velocity response and the nystagmus pattern is a canal plug by otoconia. It is thought that such a plug causes a negative cupular pressure and blocks endolymph flow (see Picture, Supplemental Digital Content 2) (Sadeghi et al., 2009). The left-beating SN in upright position was probably due to the 30° inclination of the horizontal SCC (Asprella et al., 2008), since a null point was identified with the head pitched down about 30° . As its direction was not modified by the different head positions, this nystagmus was not a *pseudo*-spontaneous nystagmus (Asprella et al., 2008). Such would be expected if the otoconia debris were to move to the most gravity-dependent part of the canal.

The asymmetrically saturated eye velocity trajectory cannot methodologically be ascribed to goggle slippage. Goggle slippage causes eye-to-head velocity asynchrony in both head movement directions rather than systematic eye velocity saturation in just one direction. In the other direction, the eye and head velocity trajectories were mirror-symmetrical. Had goggle slippage caused the observed velocity saturation, the liberatory maneuver would not have restored mirror symmetry on the affected side. This can only

be the result of a reversible biomechanical modification of the cupular-endolymph system dynamics by the canal plug.

Left saccades were also identified during left vHIT, probably corresponding to the fast phase of the left-beating nystagmus. It is possible that the head impulses generated a short, but high-amplitude increase in the level of persisting vestibular imbalance, which in turn triggered quick phases locked at 200 to 300 ms after impulse onset. A mild dynamic VOR gain asymmetry persisted on day 3, probably due to continuing changes in biomechanical SCC properties.

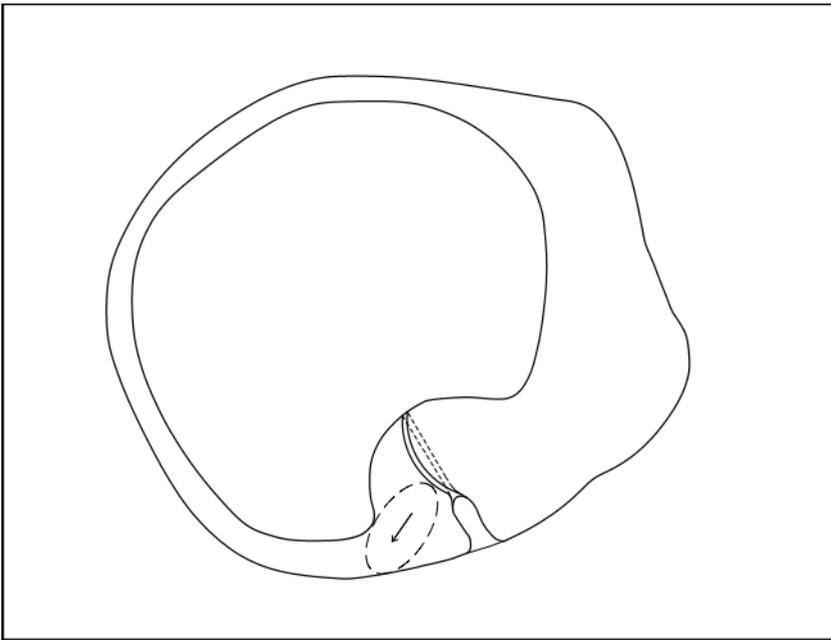


Figure 18. Proposed mechanism of cupular deflection by the plug. Cupular constant utriculofugal deflection by the plug, locking the cupula immobile and/or blocking the endolymph flow.

Horizontal semicircular canal plugging affects cVEMPs and oVEMPs.

Both cVEMPs and oVEMPs were absent on the right side at presentation and after the liberatory maneuver. This is not the first report on BPPV affecting cVEMPs. Several studies have reported that 25-35% of BPPV patients have abnormal cVEMPs (Akkuzu et al., 2006; Longo et al., 2012), but most only evaluated posterior BPPV and no oVEMP data were published.

Interestingly, the symptoms and clinical examination did not correlate with the VEMP examination: The patient was symptom-free after the liberatory maneuver. This is surprising because the current understanding is that VEMPs test otolith function. On this basis the positive VEMP result would suggest otolith dysfunction with accompanying symptoms, which, however, were not observed.

Later, VEMPs progressively normalized through day 30 to day 80. An oVEMP recovery pattern has been reported 82 days post presentation in a vestibular neuritis patient in whom it is assumed that the lesion was confined to the nerve (Manzari et al., 2011). Our case is different in that the absence of spontaneous nystagmus and vHIT normalization just after the liberatory maneuver exclude vestibular nerve involvement.

Our patient therefore had a mechanical canalar malfunction with normal vestibular nerve function. The absence of SN and the vHIT normalization after the liberatory maneuver do not suggest any other vestibular disturbances. The recovery from symptoms immediately after the liberatory maneuver raises the question of whether there was an associated otolith dysfunction at all. Such a dysfunction would necessarily have caused observable symptoms. We therefore hypothesize that SCC may contribute to VEMP responses.

The alternative explanation that the reported VEMP results are caused by an insult and early recovery of both otoliths is unlikely. It is difficult to conceive that receptor damage could recover as quickly and as completely as oVEMPs normalized. With such receptor damage ipsilateral cVEMPs and oVEMPs remained absent for at least 6 months in a patient with an acute peripheral cochleo-vestibular loss (Goto et al., 2011). The cVEMP and oVEMP recovery pattern reported here cannot be explained by the view that dynamic function of both saccule and utricle can simultaneously recover in less than 30 days (13,14). No such simultaneous recovery process is known in the literature.

The interpretation that VEMPs mainly test the otoliths relies on animal studies in which the afferent units were classified as otolithic on the basis of their responsiveness to static head tilts (Curthoys et al., 2006; Curthoys et al., 2011). This way, however, SCC units probably also entered the analysis because surgery exposed the animal labyrinth to a temperature gradient that made the SCC units gravity-dependent (Zhu et al., 2011a). A recent study that

took account of this effect provided neuroanatomical and neurophysiological evidence of a possible contribution from both the canals and otoliths to VEMP responses (Zhu et al., 2011a). Canal activation has also been proposed to be responsible for enhanced oVEMPs in superior SCC dehiscence (Welgampola et al., 2009; Aw et al., 2010). Several studies found ipsilateral cVEMP threshold lowering (Niesten et al., 2012) and oVEMP hypersensitivity (Zuniga et al., 2012) and cVEMP and oVEMP threshold normalization after superior canal plugging (Welgampola et al., 2008). Although threshold lowering and hypersensitivity of VEMP responses in the presence of canal dehiscence does not necessarily imply canal activation, it is interesting to note that the eye movements elicited in these patients occur in the plane of the affected canal. The differentially delayed normalization of both vHIT and VEMP responses after the liberatory maneuvers remains to be explained.

The second hBPPV event is in accordance with the published BPPV recurrence rates (50 % within 10 years and 80% within the first year).(1) In this episode only a mild asymmetry was noted with the vHIT, both before and after the repositioning maneuver, matching the vHIT first event results registered after the liberatory maneuver. One hypothetical explanation could be the presence of sub-clinical residual debris, which would later be cleared at day 30.

During this event no major changes were observed in VEMP responses. The persistence of cVEMP latencies asymmetry in BPPV patients has been proposed to reflect irreversible neuronal degenerative changes.(2) Gacek also reported vestibular ganglion cell loss in five temporal bones from patients with BPPV.(3) This ipsilateral latency shift is however within normal limits(4) , and was not observed in the oVEMP responses, and so doesn't suggest any pathologic significance.

Controversy on the canal origin of VEMP

An extended commentary by Professor Ian Curthoys and Dr. Leonardo Manzari (Curthoys et al., 2014) on this case-report (Luis et al., 2013) reveals the on-going controversy surrounding the hypothesis of a canal origin of VEMP to ACS. At the heart of the controversy lies the challenge that this hypothesis poses to the widely accepted interpretation that VEMP responses to ACS have an otolithic origin.

The commentary raised a number of issues related to two studies, one clinical and one basic study where click-evoked responses in vestibular afferents are investigated in rats (Luis et al., 2013; Zhu et al., 2011a). A joint reply by the authors of both studies (Luis et al., 2014) aimed to address the concerns and to clarify several important issues related to the technical aspects of VEMP testing, the time course of VEMP and VOR gain recovery in the reported patient, the observed eye velocity saturation as a possible sign for a canal plug, and to the literature on human and animal VEMP neurophysiology.

In view of the apparent dissociation between VOR and VEMP recovery times in the reported patient, the authors of the Commentary raised the issue of a “logical problem” in our conclusion. The VOR gain recovered early after treatment, while the recovery of both oVEMP and cVEMP was delayed. In our Discussion (Luis et al., 2014) we explicitly emphasized that “this differentially delayed normalization (...) remains to be explained”. Therefore, we provide the following more detailed considerations:

A possible but admittedly highly speculative explanation might be the residual mild gain asymmetry of 15% (0.81 on the right versus 1.09 on the left) reported for Day 3, i.e., 48 hours after the treatment. As can be seen in the eye and head velocity regression diagram in FIG. 1, this mild gain asymmetry is the result of a right gain deficit occurring only at head velocities above 150 °/s. In the Discussion this was attributed to “continuing changes in biomechanical semicircular canal properties”. It might well be that such a mildly reduced gain is already a sufficient condition to have an effect on the VEMPs. The interpretation in the Commentary by Curthoys and Manzari that “canal function and VEMPs returned independently” is therefore not supported by the data we presented. On the contrary: after complete recovery 80 days after treatment, a second episode with a right geotropic hBPPV, which occurred 8 months later, again showed a mild asymmetry of both VOR gain and cVEMP, which eventually recovered 30 days later. The recovery pattern in the two episodes shows that VEMPs and horizontal VOR gain are not independent, as suggested by the Commentary, but that they are associated: whenever the horizontal VOR was even mildly affected, this also had an effect on the VEMPs.

What “remains to be explained” in future work is the observation that the association of horizontal VOR with VEMPs does not seem to be a metrical one, i.e., the immediate partial recovery of VOR gain after treatment from 0.29

to 0.81 is not reflected in a comparable VEMP recovery. This might be due to a number of mechanisms, e.g., a threshold in semicircular canal biomechanics, central compensation, or frequency-dependent differences in response to 500 Hz ACS versus head impulses with a frequency content of 5 Hz. In addition, the two episodes are different in that the first event was characterized by an unusual horizontal canal plug and the second event by a more common hBPPV, which might be a reason for the dissociation of oVEMP and cVEMP between the two episodes.

A Clinical Capsule Report like ours (Luis et al., 2013) cannot provide conclusive explanations for all these observations. The observed association and its alternative explanations, however, demonstrate that the rigid assumption of an otolithic origin of VEMP responses as the only possible interpretation for the arguable independence of VOR gain and VEMP recovery does not justify a falsification of our conclusion. The controversy ensuing in both the Commentary by Curthoys and Manzari and in this reply shows how important it is for the clinical interpretation of ACS-induced VEMPs to clarify these questions in future work.

The Commentary by Curthoys and Manzari continues to cite three publications by Manzari et al. (Manzari et al., 2012a; Manzari et al., 2012b; Manzari et al., 2012c) in support of the view that a dissociation of VOR gains and BCV-induced VEMPs demonstrates the different vestibular origins of the two outcomes, with VOR gains reflecting canal and VEMPs reflecting otolith function.

The first difficulty that arises from comparing our VEMP results with those of Manzari et al. (Manzari et al., 2012a; Manzari et al., 2012b; Manzari et al., 2012c) is the difference between stimulation methods: We used air-conducted sound and the latter used bone-conducted sound.

The Commentary further claims that “all 59 patients in Manzari et al. (Manzari et al.; 2012a) had normal horizontal canal function during both vHIT and caloric testing”. However, Manzari et al (Manzari et al., 2012a) did not report that ALL 59 patients were examined with vHIT, but only that “MANY patients were also tested by video recording of horizontal head impulses”, without specifying how many patients were tested by vHIT and what their VOR gains were. Apparently, only the presence of a corrective saccade was assessed by vHIT and not the gain. From the few vHIT details reported by

Manzari et al. (Manzari et al., 2012a) it is difficult to compare their results with our quantitative vHIT analysis of VOR gain (Luis et al., 2013). Apart from VOR gain, another missing detail is head impulse velocity. In FIG. 1 of our case report (Luis et al., 2013), VEMP asymmetry on Day 3 was associated with a mild VOR gain asymmetry of 15%, which was unmasked only at head velocities between 150 °/s and 300 °/s. Whether the head impulses used by Manzari et al. (Manzari et al., 2012b; Manzari et al., 2012c) were too slow to unmask such a gain asymmetry is anyone's guess.

In the case report on a 4-year-old boy by Manzari et al. (Manzari et al., 2012c) head impulse velocity was indeed too slow to unmask even a more pronounced asymmetry. Head velocity on the affected right side reached its peak of about 80 °/s at about 90 ms after movement onset (Fig. 1). This corresponds to an estimated acceleration of roughly 1,400 °/s², which is well below the accelerations typically used in previous studies on head impulse testing. For example, Aw et al. (1996) used accelerations of 3,000 to 4,000 °/s² and Schmid-Priscoveanu et al. (2001) reported 10,000 °/s², with peak velocities of 250 °/s. In contrast, Manzari et al. (Manzari et al., 2012c) stimulated with less than a third of this peak velocity, although it is well known that only “rapid, ... unlike slow” head movements demonstrate the VOR gain asymmetry “that is expressed by Ewald's 2nd Law” (Halmagyi et al. 1990).

Since this law is fundamental to head impulse testing, a possible consequence of ignoring it is a false negative vHIT outcome, as recently demonstrated by Machner et al. (2103) in a patient with unstable gait and oscillopsia after left-side mastoidectomy for cholesteatoma. vHIT outcome in this patient was indeed negative as long as peak head velocities remained below 200 °/s. In accordance with Ewald's 2nd Law, gain asymmetry was only unmasked with head impulse velocities of 300 °/s. Therefore, the dissociation between VEMP and vHIT responses in Manzari et al. (Manzari et al., 2012a; Manzari et al., 2012c) might simply be due to false negative vHIT outcomes.

In the case report by Manzari et al. (Manzari et al., 2012b;) the vHIT results in Fig. 2 A do not support the conclusion in the Commentary by Curthoys and Manzari that the patient had normal horizontal canal function. On the contrary: The gain on the affected right side (mean=1.14, SD=0.08, N=24) was significantly smaller ($p=7*10^{-9}$, one-tailed t-test) than the gain on the left side (mean=1.35, SD=0.08, N=12). Both gains were above the

normative range of 0.78 to 1.1 (8). The gain asymmetry of 8.4% was beyond the range of normal values of <5.6% (7).

VEMP Neurophysiology – Animal Testing

Curthoys' group was the first to specifically examine the neural basis of VEMP testing by studying the responses of vestibular afferents to clinical VEMP stimuli. They reported that sound primarily activated the saccule (Murofushi et al. 1995; Murofushi et al., 1997; Curthoys et al., 2006) and utricle (Curthoys et al., 2012), but not the canals, even at intensities of 80 or 90 dB SL re ABR threshold. These seminal works have been widely cited to support the current saccular theory of cervical VEMP. While the simplicity of the saccular theory has played an important role in the rapid development of the field, it has been challenged by accumulating evidence that shows sound activation of the semicircular canals (for literature review, see Zhu et al., 2011a).

To address the neural basis of sound activation of the vestibular system, which is essential for interpreting clinical VEMP testing results, Zhu and Zhou at the University of Mississippi Medical Centre have conducted a series of studies over the past decade to further characterize the responses of the vestibular system to clinical VEMP stimuli in monkeys (Zhou et al. 2004; Zhou et al. 2005; Zhou et al. 2007; Xu et al. 2009) and rats (Zhu et al. 2010; Zhu et al. 2011a; Zhu et al. 2011b, Zhu et al. 2012a; Zhu et al. 2012b). Their efforts are motivated by three aims. The first aim is to develop a quantitative measurement of sound sensitivity of an individual vestibular neuron. This is achieved by computing the cumulative probability of evoking a spike (CPE) that measures how a transient stimulus (e.g., a brief click) induces a change of firing probability of a neuron (Broussard et al., 1992). Instead of simply classifying an afferent as sound sensitive or non-sound sensitive, the CPE analysis provides a quantitative assessment of sound sensitivity of a vestibular neuron. The second aim is to employ the CPE approach to record a large number of vestibular afferents from all the five vestibular end organs to test the saccular theory of VEMPs. The third aim is to seek sound parameters that can selectively activate certain vestibular end organs, which will serve as the neural basis of discriminative VEMP testing protocols and interpretation guidelines.

Zhu et al., cited by Luis et al. (2013) as reference 15 and in the Commentary (2) as reference 2, surveyed the sound sensitivity of over 900 vestibular afferents in anesthetized rats. In addition to activating 81% of irregular otolith afferents, acoustic clicks [80dB SL re ABR threshold (~130dB pSPL)] activate a **substantial** number of irregular anterior canal afferents (AC, 59%) and horizontal canal afferents (HC, 47%). Among them, ~ 50% of sound sensitive AC afferents and ~20% of sound-sensitive HC afferents are high sound-sensitive afferents (i.e., CPE>0.5; Figures 2 and 3 in Zhu et al., [2]), which are considered to contribute to generating VEMPs. It should be noted that the canal afferents with lower CPE values may also contribute to VEMPs because summation of synchronous activation of a population of sound-sensitive afferents may result in measurable VEMP responses.

In addition to the neurophysiological evidence of sound activation of the canals, a recent intra-axonal recording/labelling study shows that click sensitive afferents innervate the HC and AC cristae as well as the saccular and utricular maculae (22), therefore, providing direct anatomical evidence for sound activation of both the canals and otoliths. Since motoneurons of the sternocleidomastoid muscles (SCM) receive inputs from both the canals and the otoliths (for reviews, Wilson and Schor, 1999 [25]; Uchino et al, 2005 [26]), these new data suggest that the contribution of canal afferents to VEMPs should not be ruled out in clinical VEMP testing. However, given the distinct physical and geometrical properties of the otoliths and the canals, it is possible to achieve selective activation of a set of vestibular end organs by employing appropriate sound parameters (20,21,27-30) (Lewis et al., 2010; Donnellan et al., 2010, Wei et al., 2012; Ashford et al., 2013; Zhu et al., 2010; Zhu et al. 2011a). Their on-going experiments have this aim.

The Commentary also mentioned an issue related to identifying the end organ innervated by an otolith afferent. In intact animals, otolith afferents can be reliably identified by their responses to static head tilts, because canal afferents do not respond to changes in head orientation with respect to gravity. In animals that undergo surgical procedures for vestibular nerve recording, however, Goldberg and Fernandez (1975) (31) showed that the vertical canal afferents are sensitive to static head tilts because removal of the brain tissue overlying the vestibular nerves and ganglion exposes the bony labyrinth to room temperature. This results in a thermal gradient across the labyrinths, which makes the vertical canals sensitive to gravitational changes. To avoid this

ambiguity, it is important to employ turntables that provide adequate rotational stimulation to the vertical canals.

Velocity Saturation by a Canal Plug

The most puzzling remark in the Commentary by Curthoys and Manzari concerns the "final error" that we (Luis et al., 2013) are said to have made by not citing Manzari et al. (2011) as the first to "describe" the velocity saturation. This comment is puzzling because in the whole text there is indeed no description of any velocity saturation. The authors of the Commentary point to a velocity saturation in Figure 1, which, however, is characterized by the occurrence of many saccades, by slow phase eye velocities that are difficult to distinguish from saccades and "bump artefacts" (Manzari et al., 2011), by a considerable noise content, by a low image resolution, and by image compression artefacts. A velocity saturation is therefore difficult to detect. Only on the basis of this figure and without the raw data it is impossible to assess the claim in the Commentary that this figure shows a velocity saturation. If there was a velocity saturation, it went unnoticed.

Interestingly, a similar velocity saturation also went unnoticed in a surgical canal plugging (See figure S1 in MacDougall et al., 2013), which clearly supports our conclusion that this particular velocity profile might be a specific sign of a canal plug. This profile was documented both with search coil and with vHIT. The search coil recording, however, showed a clearer image of this saturation than did the vHIT recording. The difference might be due to the recognized "bump artefact" (MacDougall et al., 2013) present in the vHIT device that the authors used.

Could the contralateral inhibitory saturation be responsible for the saturation in the eye velocity profile? Evidence from vHIT testing in unilateral vestibular loss after schwannoma surgery contradicts this, as there is clearly no velocity saturation (see Figure 4 in MacDougall et al. 2013). The reason for this probably relies on the fact that each contralateral firing cell has its own firing discharge and velocity-firing characteristic. Therefore each would hit the firing rate saturation boundary at 0 Hz at another velocity. vHIT velocity saturation in vestibular neuritis seems unlikely. Instead, for us (Luis et al. 2013) the most plausible explanation for the saturation of the eye velocity response (and the nystagmus pattern) observed in the reported BPPV patient was the presence of an otoconial canal plug, since such a plug would cause a negative

cupular pressure and block endolymph flow, thus modifying the cupular-endolymph biomechanical dynamics.

With the above argumentation we addressed the arguments of the Commentary by Curthoys and Manzari (2014) in the following points:

1) We have demonstrated that a technical failure can be excluded as a possible explanation for the simultaneous absence and recovery of both cVEMP and oVEMP. Very basic technical aspects, such as the possible presence of wax in the ear canal, are not the most plausible causes for our findings;

2) vHIT and VEMP responses did not return independently but were associated. Whenever the horizontal VOR was even mildly affected, this also had an effect on VEMPs;

3) To the best of our knowledge vHIT was used for the first time to document a high-frequency VOR hypofunction during BPPV. Moreover, it documented an eye velocity saturation profile as was later demonstrated in a surgical canal plug;

4) Our case proved that a patient with BPPV may present with spontaneous nystagmus. BPPV must be ruled out in acute vestibular syndrome patients. Not only the direction but also the intensity of the nystagmus position dependency should be tested in every patient with spontaneous nystagmus, just as the vHIT velocity profile;

5) As there is solid and growing evidence of sound canal activation, canal contributions to VEMPs should not be ruled out before the neurophysiological basis of sound activation of the vestibular system is understood.

In conclusion, the observations presented here challenge the common belief that VEMPs are evoked by otolith stimulation only. In this case, the assumption of a reversible canal dysfunction by a plug offers a more plausible hypothetical explanation for all observations. In the future, the gain saturation observed with the vHIT might serve as a characteristic sign for a canal plug.

III. Topodiagnosis in non-acute vestibular lesions

1. Inferior peduncle lesion presenting with bilaterally impaired vestibular responses to horizontal and posterior head impulses

The superior vestibular nerve carries primary afferents from the anterior and lateral ampullae and the inferior vestibular nerve from the posterior ampullae. These primary vestibular afferents connect to the vestibular nuclei and the cerebellum. End-organ lesions, like vestibular neuritis, usually affect only part of the vestibular nerve, mostly the superior division, with the inferior division commonly being spared. When evaluating our patient in the physiological frequency domain with the vHIT, VOR was deficient in both horizontal and posterior semicircular canal directions and normal in both anterior SCC directions. No plausible combination of end-organ lesion, therefore, should be responsible for these observations.

The primary afferents that are destined for the cerebellum bypass the vestibular nuclei and proceed through the inferior cerebellar peduncle to the ipsilateral flocculus, nodulus, and anterior uvula.(Shinoda and Yoshida 1975) The flocculus govern by inhibition the central connections of the anterior SCC, but not the posterior canals. We speculate that this disinhibition effect could contribute to the rather compensatory eye responses in the anterior SCC direction. There was a diminished caloric response in the right side, but cerebellar lesions may increase, decrease or have no influence in VOR gain at low frequencies.(Zee et al. 1981) VEMP results also match previous results on circumscribed cerebellar lesions.(Pollak et al. 2006).

Differentiating central from peripheral origins of VOR lesions can be challenging. To the best of our knowledge, this is the first report where three-dimensional vHIT, by means of peripheral-unlikely combinations of VOR lesion, has shown to be of topodiagnostic value.

IV. vHIT topodiagnostic in hereditary cerebellar ataxias with and without involvement of central vestibular pathways.

1. Vestibulo-ocular reflex dynamics with head-impulses: slow phase and quick-eye movements in Huntington's disease

VOR seems to be preserved at physiological frequency domains in HD patients, even in more advanced stages of the disease. Although both voluntary saccades and quick phases of nystagmus are known to be slower in HD, quick eye movements triggered with impulses showed no differences in comparison to controls. Future studies should address whether gaze failure in darkness that we identified in the current study proves beneficial as a biological marker for HD.

2. Vestibulo-ocular reflex dynamics with head-impulses discriminates hereditary cerebellar ataxias

The main findings of this study are:

- 1) Most SCA and FA patients had a VOR deficit, with the exception of SCA2 patients;
- 2) VOR latency was longer in FA and SCA3;
- 3) VOR_p , VOR_{40} and VOR_{60} were both abnormally low in FA and SCA3, but only SCA3 had VOR_{80} significantly lower than controls;
- 4) Covert saccades were triggered only in SCA3 4) overt saccades were triggered in all groups, but occurrence rate and peak-velocity are negatively correlated with VOR_{40} .
- 5) VOR_r gain showed a significant negative correlation with disease severity evaluated with SARA.

VOR findings

VOR latency was significantly longer in SCA3 and FA (Fahey et al. 2008; Newman-Toker et al. 2013) than controls. Both controls and SCA-1 showed negative average values, this probably resulting from slippage and camera

mechanical inertia, but these technical issues were common to all groups. There was a consistent low VOR_p , similar to the results obtained with the search-coil technique in both FA (Fahey et al. 2008; Newman-Toker et al. 2013) and SCA3 (Gordon et al. 2008; Newman-Toker et al. 2013).

In previous reports for low-frequency VOR testing (caloric test or rotatory chair), SCA3 showed bilateral abnormal (Gordon et al. 2003; Yoshizawa et al. 2004; Park et al. 2013), SCA1 normal (Buttner et al. 1998; Gordon et al. 2003; Yoshizawa et al. 2004; Fahey et al. 2008; Zeigelboim et al. 2011) or abnormal (Klostermann et al. 1997; Bürk et al. 1999; Migliaccio et al. 2004; Szmulewicz et al. 2011b) and SCA2 normal VOR results (Buttner et al. 1998; Bürk et al. 1999; Kremmyda et al. 2012), all of these matching our vHIT findings. In contrast, caloric test and rotatory chair have mostly failed to identify the VOR deficit in FA hereby demonstrated (Ell et al. 1984; Wessel et al. 1998; Jacobi et al. 2011).

It is interesting that VOR_p , VOR_{40} and VOR_{60} were both abnormally low in FA and SCA3, but only SCA3 maintained a VOR_{80} that was significantly lower than controls. The instantaneous gain in FA did not result from the VOR latency increase, since it paradoxically showed a significant negative correlation with VOR_{80} and $VOR_{80}-VOR_{40}$ (Pearson $r=-0.87$ and $r=-0.70$, $p=0.02$ and $p=0.04$, respectively). Furthermore, VOR_{80} discriminated SCA3 from other ataxic patients with an overall diagnostic accuracy of 78%.

Catch-up saccades

To the best of our knowledge, catch-up saccades triggered with head impulses have never been explored in SCA, nor in FA patients, other than the clinical identification of overt saccades during bedside exploration (Buttner et al. 1998; Gordon et al. 2003; 2014). Overt saccade's occurrence rate and peak-velocity correlated with VOR_{40} . Still, overt saccades were present in all studied groups, though with significantly lower occurrence rate and peak-velocity in SCA2 and controls than in FA and SCA3 (**Table 11**). Nevertheless this suggests that overt saccades can be false-positive for establishing a diagnosis of a bilateral peripheral vestibular deficit in inherited ataxic patients, as it has been shown for non-hereditary ataxias (Kremmyda et al. 2012).

A central origin for covert saccades, as a VOR substitution strategy, is supported by its short latency and bilateral presence in bilateral peripheral lesions (Schneider et al. 2009; Weber et al. 2009a), though this has not been

confirmed. In this study, they were only present in three SCA3 patients, although with a lower occurrence rate and peak-velocity than in peripheral patients (Glasauer et al. 2004; Blödow et al. 2012).

The site(s) of lesion

Although described as a sign of peripheral vestibular loss, a defective HIT has been described in various cerebellar disorders. Gordon et al. (2003) (Gordon et al. 2003) described for the first time bilateral vestibular areflexia detected by the HIT, confirmed by absent responses to ice water ear irrigation, in a group of seven SCA3 patients. Further studies recording eye movements using magnetic search coils during HIT have revealed that SCA3 have low VOR gain (Gordon et al. 2008; 2014). As these patients had no symptoms or signs of auditory or other cranial nerve impairment and all eye movement abnormalities in SCA3 patients could be attributed to central nervous system dysfunction.

Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) patients (Migliaccio et al. 2004; Szmulewicz et al. 2011b) that, as SCA3, showed a caloric VOR deficit, also maintain or decrease VOR gain during the impulse and trigger covert saccades (Szmulewicz et al. 2011b; Kremmyda et al. 2012). The histopathology study of one of these CANVAS patients (Szmulewicz et al. 2011a) has shown normal vestibular end-organs but bilateral atrophy of the vestibular nerve, as well as cerebellum involvement, both also known to be affected in SCA3 (Rüb et al. 2004).

On the other hand, CANVAS that, as FA, may show normal caloric results (Ell et al. 1984) also maintain or increase VOR gain during the impulse and trigger no covert saccades. While we could not find histopathology studies in normal caloric CANVAS patients, they are presumed as pure central dysfunction patients (Kremmyda et al. 2012). Furthermore, FA patients' temporal bones have shown relatively spared end organs and vestibular nerves (Spoendlin 1974; Igarashi et al. 1982). The different involvement of both peripheral and central vestibular system structures may therefore justify this low and high frequency VOR dissociation, VOR gain dynamics and covert saccade triggering strategy as well as the dependency of these results on disease progression (Monday et al. 1984).

Clinical correlation

A negative correlation between VOR_r gain and SARA score raises the possibility of using VOR gain as a neurophysiologic biomarker for disease severity as it has recently been suggested for SCA3 (Gordon et al. 2014). FA reached the highest scores in SARA evaluation, with most of ataxic patients presenting symptoms of severe unbalance and gait difficulties. Visuo-vestibular symptoms of bilateral VOR loss such as oscillopsia (Bronstein 2004) were mostly absent in FA and SCA3 matching previous reports (Fahey et al. 2008). Since covert saccades were in most cases not triggered by SCA3 or FA patients, saccadic suppression is not responsible for the absence of visuo-vestibular symptoms in these groups, as has previously been suggested for peripheral vestibular patients (Macdougall and Curthoys 2012) and an alteration in perception is a more likely explanation (Hocking et al. 2010).

In summary, our findings demonstrate that vHIT supplies phenotypic hallmarks that discriminate the most common autosomal ataxias and may serve as a strategy to orient genetic diagnosis.

Concluding Remarks And Future Perspectives

Although vHIT has been used only since 2008 (Lehnen et al. 2008; Bartl et al. 2009; Weber et al. 2009), a growing number of neurophysiological studies undertaken with this new method already have shed some light (and debate) on the functioning of the vestibular system circuitry, both in acute and in chronic peripheral and central vestibular disorders. As a whole, they still represent a small portion of the total number of studies done with head impulses, both clinically and with search coil. This soon should change, since the portability, cost and patient comfort clearly surpass the gold-standard search coil limitations for clinical routine use. This should allow not only larger scale cohort studies in many diseases and conditions, namely during the acute stages, but also from new eye movement researchers, from different scientific fields, motivated by the vHIT capabilities. Nevertheless, the inclusion of vHIT into the daily neurological and neurootological clinic already allows quick and reliable vestibular evaluation, quantitatively assessing the functional state of each semicircular canal, something until now only possible in few and highly specialized eye movement labs.

To the best of our knowledge, the experiences reported here were the first to address particular vHIT technical aspects of slow phase gain and quick eye movement analysis but also clinical relevant data as the use of anti-compensatory quick eye movement and particular slow phase profiles in topodiagnosis. Moreover we were also the first to address the use of vHIT in hereditary neurodegenerative disorders.

The most relevant conclusions from this work are:

1. Quick eye movements with head impulses are present in normal subjects.
2. Slow phase regression gain and gain asymmetry between sides are already in clinical use, namely for vertical canals, yielding neurophysiologic information.
3. AQEM, Anti-compensatory quick eye movement, are a sign of peripheral vestibular dynamic imbalance in spontaneous nystagmus, with topodiagnostic value in acute vestibular syndrome patients.

4. Slow phase gain dynamics analysis in a SCC plug may show a characteristic reversible saturated eye velocity trajectory with head impulses
5. BPPV patients may present with spontaneous nystagmus, supposedly through cupular constant utriculofugal deflection.
6. Cervical and ocular VEMP may have a semicircular canal origin and not be of exclusive otolithic origin
7. vHIT supplies phenotypic hallmarks, both at the slow phase as well as at QEM level, that discriminate the most common autosomal ataxias

Many questions remain to be answered, however, and further research is required, namely to clarify the physiological mechanisms underlying the oculomotor responses to head impulses. It is now unanimously accepted that the VOR slow phase with passive head impulses results mainly from vestibular stimulation, as the contribution from vision and the cervico-ocular reflex takes place much later, even in patients after vestibular loss (Halmagyi et al. 1990a). With regard to catch-up saccades, namely covert-saccades, there still is no consensus on what triggers this effective image stabilization strategy. Evidence from coil studies suggests that covert saccades require visual input, at least in complete BVL, so that a basic reflexive visual-to-ocular motor mechanism, which later could be improved by practice, could be behind this vestibular substitution strategy. Although it is well established that visual input is crucial for compensation, the residual vestibular function also could help trigger these short-latency catch-up saccades (Lehnen et al. 2013). Others have suggested a neck-to-ocular motor mechanism (Macdougall and Curthoys 2012). We are currently working on a motionless head impulse paradigm, where only visual stimulation is supplied to BVL patients. Preliminary results point to a visual contribution to slow phase generation, both in terms of latency and gain dynamics, as well as to covert saccade generation in these patients. Given the short latencies an eye following reflex may be behind these responses. The clarification of these strategies should improve the vestibular rehabilitation approach in BVL and UVL patients, as a locked, isochronous pattern of refixation saccades in vHIT is associated with lower DHI scores (Batuecas-Caletrio et al. 2013).

The search for an algorithm that can differentiate CNS from peripheral lesions, particularly in acute vestibular syndromes (Newman-Toker et al. 2013),

is also a work in progress, and results on slow phase, but also quick eye movement characteristics, have been promising. Behind the obvious, non-compensatory slow phase eye velocity profiles that predominantly should point to a peripheral AVS origin we have raised the interest in overt anti-compensatory QEM, as a sign of peripheral dynamic asymmetry in AVS (Luis et al. 2014c) as others later demonstrated in covert AQEM, in non-acute patients, here with the potential to differentiate MD from vestibular migraine (Heuberger et al. 2014). Very recently, in a study with coils (Chen L, Todd M, Halmagyi G, Swee Aw, 2014), the value of QEM in topodiagnosis of AVS patients has been confirmed. In the same work AQEM were also reconfirmed as a vHIT recording of modulated spontaneous nystagmus.

One of the major problems persisting when analysing data from the vHIT is to avoid and recognize artefacts (Macdougall et al. 2013b). Video-oculography (VOG) devices are very sensitive to camera slippage, which can be caused by the inertia of the camera when the head is moving at high accelerations, as is the case in head impulse testing. Since the resulting pupil displacement is indistinguishable from a real eye movement VOG devices mistake camera slippage for eye rotation.

Testing procedures also differ significantly and different algorithms have been used to estimate VOR function. These need to be compared both to video and coil data but also between themselves – are they both effective at detecting and quantifying a vestibular loss, or are we just circularly comparing methods? These studies are necessary so that guidelines for the testing procedure and interpretation, their role and normality values promptly are established.

A common flaw that also still persists is the search to determine how effective vHIT is in detecting a caloric hyporesponsiveness, so to substitute calorics with vHIT completely at the clinical level. It is difficult to conceive that a future test will be able to answer that question better than the caloric test itself. The question, therefore, should be slightly redirected, as to how effective vHIT is in evaluating the selective high frequency functional state of each SCC.

In conclusion, the vHIT allows the quantification of oculomotor responses with head impulses. It is, therefore, an objective measure of the oculomotor response to a physiological vestibular stimulus, i.e., the high-

frequency rotational acceleration inputs detected by SCC. It is particularly useful in the bedside evaluation of acute patients with spontaneous nystagmus and it has topographic value. Since this technology permits the analysis, re-analysis and easy share of data, thorough knowledge should be made available quickly, allowing for a better phenotypic and topographic characterization of the several aetiologies of vertigo and dizziness.

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- Zhu H, Tang X, Mustain M and Zhou W. Air-conducted click-evoked responses in the vestibular nuclei of rats. Program No. Neuroscience Meeting Planner. New Orleans, LA Society for Neuroscience, 2012.
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- Zhu H, Tang X, Wei W, Mustain M and Zhou W. Air-conducted short tone bursts-evoked vestibular responses in rats. Program No. 579.05/FF12 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience, 2011.
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Appendix

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List of publications.

Full papers in indexed journals

1. **Luis L**, Benzinho T., Ferreira N., Vaz Garcia. Postural adaptations under virtual reality, saccadic and optokinetic visual stimulation. *Ann. N.Y. Acad. Sci.*, 2011 vol 1233(1) ev supl
2. **Luis L**, Costa J, Vaz Garcia F, valls-Solé J, Brandt T, Schneider E. Spontaneous Plugging of the Horizontal Semicircular Canal With Reversible Canal Dysfunction and Recovery of Vestibular Evoked Myogenic Potentials. *Otol Neurotol.* 2013; 34(4):743-7.
3. **Luis L**, Zhu H, Costa J, et al. Reply to the commentary on Luis et Al. "Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials". *Otol Neurotol.* 2014; 35(2):379–383.
4. **Luis L**, Costa J, Yacovino D, A pragmatic strategy for positional downbeat nystagmus and vertigo. *Otol Neurotol* 2015 (accepted for publication)
5. **Luis L**, Lehnen N, Muñoz E, de Carvalho M, Schneider E, Valls-Solé J, Costa J Anticomensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus. *Vest Research* 2015 (accepted for publication)
6. Maia F, **Luis L**. Inferior peduncle lesion presenting with bilaterally impaired vestibular responses. *Laryngoscope* 2015 (accepted for publication)
7. **Luis L**, Costa J, Muñoz E, de Carvalho M, Lehnen N, Carmona S, Schneider E, Gordon C.R, Valls-Solé J. Vestibulo-ocular reflex dynamics with head-impulses discriminates hereditary cerebellar ataxias. *Vest Research* 2015 (submitted, under peer review)
8. **Luis L**, Costa J, Mossman S, Lehnen N, Jahn K, Schneider E. Human vestibulo-ocular reflex dynamics examined through the

video Head Impulse Test. Clin Neurophysiol 2015 (submitted,
invited review)

Book chapters and monographies

1. **Luis L**, Ferreira N. 2012. Reabilitação vestibular de deficits vestibulares agudos e subagudos. in Reabilitação Vestibular. APO.
2. **Luis L**, Petrak M. 2013. Balance and Dizziness: Introduction to Video Head Impulse Test (vHIT), Interacoustics.
3. **Luis L**. 2014. The video Head Impulse Test. In: Carmona S., Asprela Libonati G., eds. Neurotology. Akadia Editorial; [CD-ROM].
4. **Luis L**. 2014. O vHIT como teste de avaliação vestibular. In: Zuma e Maia F., Mangabeira Albernaz P., Carmona S., ed. Otoneurologia Atual. Revinter;pp 89-104.

Online Publications

1. **Luis L**. 2012. Subjective visual vertical, Curso de e-learning sobre Exploração Funcional Vestibular. Retrieved from: <http://elearning-abbott.dlc.pt>
2. **Luis L**. 2013. Video Head Impulse Test, Curso de e-learning sobre Exploração Funcional Vestibular. Retrieved from: <http://elearning-abbott.dlc.pt>
3. Yacovino D., **Luis L**. 2014. Pharmacologic Treatment Of Vestibular Disorders. Vestibular Disorders Association. Retrieved from: http://vestibular.org/sites/default/files/page_files/Documents/Pharmacologic%20treatments.pdf

List of scientific presentations and abstract publications.

1. Postural Adaptations Under Virtual Reality, Saccadic And Optokinetic Visual Stimulation, Ocular Motor And Vestibular Research Symposium-Tribute To John Leigh, Buenos Aires, Argentina, 2011. (Oral Presentation).
2. Relative Cochlear And Vestibular Ototoxicity Produced By Transtympanic Gentamicin Under Recombinant Human Erythropoietin Cytoprotection In The Rat. 48th Inner ear Biology workshop, Lisboa, Portugal, 2011. (Oral Presentation).
3. Vestibular rehabilitation under virtual reality immersion. Encontro nacional de Otoneurologia, Troia, 2011. (Oral Presentation).
4. Vestibular Neuritis Recovery: The vHIT Dynamic Perspective. Prosper Ménière Conference, Austria, 2012. (Oral Presentation).
5. vHIT as a diagnostic tool (Masterclass). Seoul National University College of Medicine, Seoul, South Korea, 2012. (Invited speaker)
6. Jamming do canal semicircular horizontal com disfunção canalar reversível e recuperação dos potenciais evocados miogénicos oculares e cervicais. Congresso Iberico Otoneurologia, Porto, Portugal, 2012. (Oral Presentation).
7. Video Head Impulse Test como teste diagnóstico em patologias vestibulares periféricas e centrais. Congresso Iberico Otoneurologia, Porto, Portugal, 2012. (Oral Presentation).
8. Spontaneous plugging of the horizontal semicircular canal with reversible canal dysfunction and recovery of vestibular evoked myogenic potentials. XXVII Barany Conference, Upsala, Sweden, 2012. (Oral Presentation).

9. Russian Neurology Congress, Nizhny Novgorod, Russia, 2012. (Invited Speaker).
10. vHIT como instrumento de avaliação vestibular, Congresso Luso-Brasileiro de Otoneurologia, Fortaleza, Brazil, 2012. (Invited Speaker)
11. Video Head Impulse test como instrumento de exploración vestibular. 63 Congreso nacional SEORL, Oviedo, Spain, 2012. (Instructional Course)
12. vHIT as a diagnostic tool, 16th International Conference IAPA, Beijing, 2012.
13. Fisiología Vestibular 2012, Estado del Arte del Estudio de la Función Vestibular. LXIX ENT Congress, Concepcion, Chile, 2012. (Invited speaker)
14. Conceptos y Manejo actual del VPPB, International faculty of LXIX ENT Congress, Concepcion, Chile, 2012. (Invited Speaker)
15. Diagnostics and treatment of vertigo – International practice. vHIT as a diagnostic tool. Moskow, Russia, 2012. (Invited Speaker)
16. vHIT as a diagnostic tool (Masterclass). American Balance Society Meeting, Scottsdale, EUA, 2013. (Invited speaker)
17. Vestibular-ocular reflex dynamics with head-impulses discriminates hereditary cerebellar ataxias, Congresso de Neurologia, Lisboa, 2013. (Oral Presentation).
Sinapse 2013; 2(13):79-80
18. Topodiagnóstico en Síndrome vestibular agudo (Masterclass). 64 Congreso nacional SEORL, Madrid, Spain, 2013. (Invited Speaker)
19. Video Head Impulse test como instrumento de exploración vestibular,. 64 Congreso nacional SEORL, Madrid, Spain, 2013. (Instructional Course)

20. Anticompensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus. 9th Meeting of the British Society of Neuro-otology London, 2013. (Oral Presentation)
21. vHIT as a diagnostic tool (Masterclass). Postgrado en Neurología, Pre-programa Master en Diagnostico Electrodiagnostico neurologico, Universidade de Barcelona, 2013. (Invited Speaker)
22. Central or Peripheral vertigo? New Insights from Video Head Impulse Test. 10th Annual Middle East Update in Otolaryngology Conference, Dubai. 2013. (Invited Speaker)
23. BPPV diagnosis and treatment – Current concepts. 10th Annual Middle East Update in Otolaryngology Conference, Dubai. 2013-. (Invited Speaker)
24. Meniere’s disease: A Controversial Diagnosis of exclusion. 10th Annual Middle East Update in Otolaryngology Conference, International Faculty. Dubai. 2013. (Invited Speaker)
25. Benign Positional Vertigo. 10th Annual Middle East Update in Otolaryngology Conference, Dubai. 2013. (Instructional course)
26. Vestibular Evaluation Update. 10th Annual Middle East Update in Otolaryngology Conference, Dubai. 2013. (Invited Speaker)
27. Diagnostic Approach to Vertigo and Dizziness in Children. 10th Annual Middle East Update in Otolaryngology Conference, Dubai. 2013. (Invited Speaker)
28. Curso de actualización de en el diagnóstico clínico del balance y vértigo y su rehabilitación, Santiago, Chile , 2013. (Invited Speaker)
29. vHIT as a diagnostic tool. First otoneurology and audiology international conference, Mexico city, 2013. (Invited Speaker)
30. Acute Vestibular Syndrome (Masterclass). National ENT conference, Romania, 2013. (Invited Speaker)

31. Vestibular ocular reflex dynamics during passive head-impulses: slow phase eye velocity and saccadic response profiles in central and peripheral vestibular lesion patients. European Neurology Society meeting, Barcelona, 2013. (Poster presentation)
Luis L. et al. P787: J Neurol 2013; 260(suppl 1): 206

32. Rapid eye-movements triggered during head impulses differentiate peripheral and central patients with spontaneous nystagmus. European Neurology Society Meeting, Barcelona, 2013. (Oral presentation)
Luis L. et al. O235: J Neurol 2013; 260(suppl 1): 16

33. Video Head Impulse Test. Portuguese National ENT Congress, Porto, Portugal, 2013. (Instructional Course)

34. New technologies in vestibular testing, round-table, IFOS-world ENT conference. Seoul, 2013. (Invited Speaker)

35. Vertigo and dizziness course, Guanzhou, China, 2014. (Invited Speaker)

36. The vestibulo-ocular reflex in vertigo, dizziness and balance disorders (Masterclass). Brainstem Society Meeting. Berlin, 2014. (Invited Speaker)

37. Vestibular ocular reflex dynamics with head-impulses in hereditary cerebellar ataxias. ICCN 2014. Berlin, 2014. (Poster presentation)
Luis L. et al. P322: Clin Neurophysiol. 2014;125:S134–5.

38. Anticompensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus. ICCN 2014, Berlin, 2014. (Poster presentation)
Luis L. et al. P323. Clin Neurophysiol. 2014; 125:S135.

39. Anticompensatory quick eye movements after head impulses: a peripheral vestibular sign in spontaneous nystagmus. XXVIII Barany Conference, Buenos Aires, Argentina, 2014 (Oral presentation)

40. vHIT instruction course.. XXVIII Barany Conference, Buenos Aires, Argentina, 2014 (Invited speaker; member of the Scientific and Organizing Committee).
41. Vestibular Ocular Reflex dynamics during passive head-impulses: slow phase and quick-eye movements in Huntington's disease. EHDN2014, Barcelona, 2014 (Poster presentation)
42. Video Head Impulse Test. Portuguese National ENT Congress, Lisbon, 2014. (Instructional Course)
43. Vestibular Update. 65 Congresso nacional SEORL, Madrid, Spain, 2014. (Instructional course)
44. Oculomotor approach to diagnosis and treatment of dizzy patient, 5th Emirates Rhinology and Otology Congress 2015, Dubai (Invited Speaker)

List of courses as main speaker.

1. Vertigo and Dizziness Course, Mexico City, Mexico, 2011
2. Vertigo and Dizziness Course, Santiago, Chile, 2011
3. Vertigo and Dizziness Course, Kuala Lumpur, Malasia, 2012
4. Vertigo and Dizziness Course, Bogotá, Colômbia, 2012
5. Vertigo and Dizziness Course, Singapore, 2012
6. Oculomotricidade em Neurotologia, Porto, Portugal, 2012
7. Curso de Vertigem e desequilíbrio, Funchal, Madeira, 2012

8. Vertigo and Dizziness Course, Xangai, China, 2012
9. Vertigo and dizziness course, Goa, Hyderabad, Calcutá, India, 2012
10. Vertigo and dizziness Course, Dubai, 2013
11. Vertigo and dizziness course, Hangzhou, China, 2014
12. Vertigo and dizziness course, XI'an, China, 2014
13. 1st international Vestibular Diagnosis, Treatment and Rehabilitation Course, Lisbon, Portugal, 2014
14. 2nd International Vestibular Diagnosis, Treatment and Rehabilitation Course, Lisbon, Portugal, 2014
15. Arts of Diagnosis and Management of Dizzy Patient, Dubai, 2015
16. 3rd International Vestibular Diagnosis, Treatment and Rehabilitation Course, Lisbon, Portugal, 2015
17. Curso de Diagnóstico, Tratamento e Reabilitação vestibular para Médicos de Medicina Geral e Familiar, Lisboa, Portugal, 2015

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