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Six-canal video-Head-Impulse-Test in patients with labyrinthine and retro-labyrinthine pathology: detecting vestibulo-ocular reflex deficits

Running Title: vHIT detects VOR deficits

Authors: Georgios Kontorinis, MD, Hiteshkumar Tailor, MSc Theofano Tikka, MSc, Mohd Afiq Mohd Slim, MSc

Department of Otolaryngology, Head and Neck Surgery, Queen Elizabeth University Hospital,
Glasgow, United Kingdom

Corresponding author

Georgios Kontorinis, MD, MSc, FRCS(ORL-HNS)

Department of Otorhinolaryngology–Head and Neck Surgery

Queen Elizabeth University Hospital

1345 Govan Road

G51 4TF, Glasgow

United Kingdom

Email: gkontorinis@gmail.com

Tel. No.: 00441413478029

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Six-canal video-Head-Impulse-Test in patients with labyrinthine and retro-labyrinthine pathology: detecting vestibulo-ocular reflex deficits

Abstract

Background: Abnormal gains in six-canal video-Head-Impulse-Test (vHIT) are attributed to semi-circular canal deficits. However, as vHIT responses are linked to vestibulo-ocular reflex (VOR), we hypothesized that abnormal gains can be due to VOR pathway deficits.

Methods: We compared vHIT gains and correlations between them (Mann-Kendall trend test) in 20 patients with superior semi-circular canal dehiscence (SSCD; labyrinthine cause) and 20 side and gender-matched patients with vestibular schwannomas (VS, retrolabyrinthine cause).

Results: VS but not SSCD was significantly associated with abnormal lateral (OR: 9.00 (95% CI:1.638;49.44), p:0.011) and posterior canal status (OR: 9.00 (95% CI: 2.151;37.659), p:0.003). In VS we found a statistically significant degree of dependence between all ipsilesional canal vHIT gains; such dependence was not observed in SSCD.

Conclusions: VOR gains differ in patients with labyrinthine and retrolabyrinthine disease, suggesting that abnormal gains can indicate not only deficits in the semi-circular canals but also elsewhere along the VOR pathway.

Key words:

Acoustic neuroma; Head-Impulse Test; Labyrinth; Vertigo; Vestibulo-ocular reflex

Introduction

Dizziness is one of the commonest presenting symptoms affecting approximately 20-30% of the population while dizziness of peripheral/ vestibular cause is believed to affect 5% of the population every year [1, 2]. These figures highlight the significance of dealing with the dizzy patient in a timely and efficient manner. While the detailed medical history and clinical examination are paramount in identifying the underlying cause, setting the precise diagnosis can be, although always crucial for tailored and prompt management, challenging requiring vestibular testing. Among the available assessment batteries, the relatively recently introduced six-canal video-Head-Impulse-Test (vHIT) has been gaining popularity, mainly due to its ease of use and applicability as well as its well-tolerated by the patient nature [3-6].

The concept of vHIT is based on the vestibulo-ocular reflex (VOR). During VOR the visual stimuli reaches the inferior olivary nucleus, transmitting the signal to the vestibulo-cerebellum that subsequently turns this signal to the vestibular nucleus alternating the sensitivity of the vestibular input [7]. In simple words, if the head of an individual whose gaze is fixed on a target is suddenly and rapidly passively rotated horizontally to one side and back, the individual will continue staring at the target, as the eye movement will instantly oppose to the head movement. This is due to the VOR and would correspond to a head movement to eye movement ratio (gain) of 1 [3, 4, 7]. Should there be a deficit in the VOR, then this response will be abnormal, as the eyes will follow the head movement with some delay; the eyes will lose fixation. This delay will be picked up by the vHIT shown as abnormal VOR gain (head to eyes movement ratio is not 1 anymore) but also will reflect in the presence of overt and covert saccades, where overt saccades are refixation attempts occurring after head movement comes to rest and covert are those occurring during head motion [3-7]. It is believed that this presence of overt (and covert) saccades with abnormal VOR gain is considered a sign of canal paresis [3, 4, 8].

While Head Impulse Testing was first described three decades ago as an experimental vestibular assessment, it was not until nearly twenty years ago when a head-mounted camera for ocular tracking led to the evolution of vHIT, which is now more widely utilised [9]. While abnormal VOR gains accompanied by overt/ covert saccades are believed to show semi-circular canal responses, the studies

that have led on standardisation of the technique as well as set the normal range are based on predominantly underpowered cohorts with an heterogeneous group of patients with various vestibular pathologies [10, 11]. This study heterogeneity can generate questions about the precise meaning of abnormal vHIT responses.

In the current study, based on the concept that the vHIT records VOR gains, we compared the vHIT gains between patients with definite labyrinthine pathology and patients with definite retrolabyrinthine disease. Our primary aim was to identify whether vHIT responses differ between labyrinthine and retrolabyrinthine pathologies. Meanwhile, our secondary aim was to assess whether vHIT gains indicate only semi-circular canal deficit/responses or responses generated along the VOR pathway rather by the peripheral vestibular organ. This is to our knowledge, the first study assessing the precise origins of the vHIT responses.

Materials and Methods

Study Settings and Patient Selection

We carried out a retrospective, case control study in tertiary, academic settings. The study was approved as an audit by the Research Ethics Committee; Caldicott's guardian approval was also granted (1008/2021).

We identified 20 patients with unilateral superior semi-circular canal dehiscence (SSCD) as defined through the clinical and audiological findings, high-resolution computed tomography of the temporal bones and cervical evoked myogenic potentials. All the patients with SSCD were identified through our tertiary referral pathway/ records and were under the care of the first author. The patients with SSCD were defined as the group of definite labyrinthine pathology due to the definite anatomic cause of their symptoms. None of the patients with SSCD have had any surgical treatment at the time of the vHITs.

We also included an equinumerous group of patients with unilateral vestibular schwannomas (VS), as determined by magnetic resonance imaging pre- and post-gadolinium administration. These patients were also identified through our tertiary database of patients with VS, covering a population of 2.2 million and were matched to the SSCD group for gender and side of the pathology. The VS group was defined as the group of definite retrolabyrinthine cause. None of the patients with VS have had any previous treatment for their tumour.

While we recognise that patients with VS can have a more complex nature of their balance problems, affecting both the labyrinth and the retrolabyrinthine vestibular pathway, we used patients with VS as the retrolabyrinthine group, given the definite location of the pathology (and accepting it as weakness of the study).

We did not include patients with vestibular symptoms of other cause to ensure the definite diagnosis as well as the appropriate classification in labyrinthine and retrolabyrinthine causes. On these grounds, we did not include patients with labyrinthitis or vestibular neuronitis to avoid equivocal diagnoses though retrospective review of the medical notes. We also excluded patients with vestibular migraines due to inability to identify an abnormal (affected) and normal (unaffected) side; on the same grounds, we

excluded patients with bilateral vestibular pathology/ failure. Patients with benign paroxysmal positional vertigo were also excluded due to the intermittent, short lasting character of their symptoms. Finally, we also excluded patients with visual pathologies that could have affected the vHIT process/ results.

vHIT Settings

Patients were sat upright in a chair 1.5 metres from a fixed point on a wall. They were fitted with the ICS Impulse® goggles connected to a computer running the accompanying OTOsuite® software (Otometrics UK (Natus Nicolet UK Ltd), Northamptonshire, UK).

The procedure of testing with vHIT has been previously well described [3, 12]. For lateral canal testing, the patient's head is briefly turned laterally abruptly 10-20°. For left anterior and right posterior canals, the head is turned to the right approximately 45° to the right, then briefly tilted abruptly 10-20°, while for the right anterior and left posterior canals, this is repeated with the head turned approximately 45° to the left. Brief upward tilting stimulates the left posterior, whereas downward tilting stimulates the right anterior. Head movements were performed at a recommended minimum velocity of 120° per second for the lateral canals, and 100° per second for the anterior/posterior canals [12], while in most of the enrolled cases, a velocity of 200° per second was preferably used to minimise any performance bias.

Six-canal VOR gains and raw data wave patterns (overt/ covert saccades) from vHIT reports of each patient were recorded and reviewed; we set the normal gain as 0.8-1.2 as per manufacturer [12].

Recorded Data and Statistical Analysis

We recorded basic demographic data, namely age at the time of vHIT testing, side of the pathology and gender as well as VOR gains for all six canals as above.

We used JAMOVI (version 1.6) to analyze the data. Numerical data were assessed for normal distribution with the Shapiro-wilks test and subsequent analyzed with Welch's T-test (t) or Wilcoxon rank-sum test (w). Categorical data were explored with Fisher's exact (f) or Chi-squared test (χ^2) and subsequently reported as Odd Ratio (OR) when statistically significant differences were noted. The

Mann-Kendall trend test (Tau-B) was subsequently performed to further explore the presence of correlation between the ipsilesional canals vHIT gains. Statistically significant p-value was set at $p \leq 0.05$.

Results

Basic Demography

We evaluated 40 patients in this study; 20 patients with unilateral SSCD and 20 patients with unilateral VS (Table 1). There were no statistically significant differences in gender and pathological side within this sample (Table 1). SSCD cohort was, however, younger than VS (<0.001). None of the included patients had any active treatment of their pathology at the time of the vHIT; however, all patients were treated accordingly at a later stage, either conservatively or surgically. The management modality is out with this work's aims.

vHIT Gains Analysis

There were statistically significant differences for the lateral semi-circular canal and posterior semi-circular canal between the VS and SSCD group (Table 2). Based on the lateral semi-circular canal vHIT gains, the presence of VS decreases the vHIT gains statistically in the ipsilesional and normal side (Table 2) compared to SSCD.

Contrary, in the posterior semi-circular canal, only the ipsilesional vHIT gains were statistically reduced compared to SSCD (Table 2). Based on categorical data, VS is significantly associated with abnormal Lateral SCC status (OR: 9.00 (95% CI:1.638;49.44), $p:0.011$) and Posterior SCC status (OR: 9.00 (95% CI: 2.151;37.659), $p:0.003$). No differences were noted in the superior semi-circular canal.

Correlation of Ipsilesional vHIT Gains

In VS, a statistically significant degree of dependence between all ipsilesional semi-circular canal vHIT gains was appreciated (Table 3, Figure 1) with the strongest correlation between the lateral and posterior semi-circular canal. Meanwhile, there was only a statistically significant negative correlation between the superior and lateral semi-circular canal in SSCD (Table 3, Figure 1).

Overall, there were abnormal responses in both groups with those being more common in patients with VS; additionally, we identified a correlation of the VOR gains between the ipsilateral canals as recorded by vHITs in patients with VS (retrolabyrinthine disease) but not in patients with SSCD (labyrinthine

disease); in particular, the gains of the lateral canals correlated with the gains from the ipsilateral posterior but also superior canals in patients with VS; this was not observed in patients with a labyrinthine cause.

Discussion

Main findings

In the present study we assessed the VOR gains as recorded through six-canal vHITs for two distinguished groups of patients, one with definite labyrinthine pathology and one with definite retrolabyrinthine pathology. We showed, to our knowledge for the first time, that in patients with a VS (retrolabyrinthine cause), there is a statistically significant dependence between all ipsilateral canal gains, while this is not the case in patients with SSCD (labyrinthine cause). Additionally, abnormal VOR gains were more frequently observed in patients with VS than with SSCD. Based on our findings, this dependence and correlation of VOR gains in patients with retrolabyrinthine disease could indicate a retrolabyrinthine origin of the vHIT responses; in simple words, abnormal vHIT gains might not necessarily indicate deficit of the semi-circular canal function only, rather a deficit along the VOR pathway.

On the hypothesis that abnormal VOR gains do not necessarily originate from the labyrinth

Previous studies have shown abnormal vHIT responses in patients with VS can have an impact on the labyrinth but also symptoms due to the affected nerve [9, 13]; as most VS tend to originate from the inferior vestibular nerve, which innervates the posterior semi-circular canal, abnormal VOR gains from that canal were expected [9, 14]. Additionally, abnormal VOR gains can be seen in asymptomatic patients with VS, indicating a subclinical deficit [9]. With respect to SSCD, vestibular symptoms can have an intermittent character, despite symptoms such as oscillopsia and pressure/ noise induced vertigo being present on a regular basis [15-17]. As such, one could use this intermittent character of the vestibular symptoms in SSCD as a possible answer to explain the abnormal vHIT responses more in VS than in SSCD patients. However, both VS and SSCD are constant and definite as a pathology, but with intermittent symptomatology nature, particularly when it comes to vestibular symptoms. On these grounds, the intermittent nature of symptoms does not seem an adequate explanation of our findings. As previously reported, vHIT records VOR gains [3-8]. On these grounds, it is sensible to hypothesize that abnormal responses can indicate a deficit along the reflex pathway rather than the canals

themselves; we do stimulate the semi-circular canals to get a response, but the response is generated by the VOR pathway. While abnormal VOR gains are believed to indicate canal deficits [3, 4, 18], which can be the case, the significant dependence between all semi-circular canals in patients with retrolabyrinthine pathology and the absence of such correlation in labyrinthine disease, raise the hypothesis of abnormal VOR gains indicating a deficit at a retrolabyrinthine level (for example in VS, the vestibular nerve) and not necessarily the canals in isolation.

While vHIT has been developed and marketed as a tool for six-canal assessment, the underpinning physiology is that of canal asymmetry. Caloric testing was traditionally reported with percentage paresis, and so perhaps vHIT should follow suit with gain asymmetry (eg. Laterality of Gain) [9].

Finally, one could claim that even in patients with VS, the vestibular symptoms relate to the impact of the size/ growth of the tumour on the inner ear/ vestibule and not on the vestibular nerve per say; therefore, it is not solely a retrolabyrinthine cause. However, the impact of the VS on the vestibular nerve has been well shown through numerous surgical and clinical studies [13, 14, 19].

Given the complexity of the vestibular pathways, we can only support our hypothesis with our present findings rather than prove it. If vHITs only indicated abnormal canal responses, then one would have expected similar relations/ dependence between the VOR gains from each canal regardless the location of the cause. However, as this relation/ dependence differs between labyrinthine and retrolabyrinthine cause (dependence present only in a retrolabyrinthine cause), it is sensible to assume that abnormal vHIT gains can indicate a deficit at a retrolabyrinthine level, too.

Strengths and limitations

The main weaknesses of our study are its retrospective bias and the small cohort size. As reported above, most studies validating and standardising vHIT measurements have so far been based on even smaller cohorts. Given the selected groups, one with patients with VS and one with patients with SSCD, which are both relatively uncommon pathologies, our enrolled numbers are significant.

As per our methods, we accepted the limitations of using patients with VS as the retrolabyrinthine group; we do recognise that vestibular issues in this group of patients can be complex; however, there is anatomically a clear retrolabyrinthine cause.

While we did not include a control group without any symptoms at all, due to ethical limitations. we used case control settings and carefully selected our patients limited to definite labyrinthine and retrolabyrinthine pathology; we excluded patients with other types of vestibulopathies, where the diagnoses, particularly on retrospective settings can be vague and debatable; this way we attempted to overcome our relatively small sample and any bias related to the retrospective character of our study. While, one could argue that we only included two groups (two types of diagnosis) as a limitation, we consider this patient selection a strength of our work as it helped us avoid misdiagnoses. What is most important, this is a novel study suggesting the hypothesis on the (along the VOR pathway) origins of the vHIT responses; while we recognise the challenges in interpreting the presented correlations, these findings should trigger further research.

Conclusion

We found correlation in the vHIT responses between the semi-circular canals with a statistically strong dependence in patients with retrolabyrinthine pathology; we did not identify similar patterns in a labyrinthine cause. These results highlight how the VOR gains from the semi-circular canals as well as the correlations between them can differ in patients with labyrinthine and retrolabyrinthine disease but also support the hypothesis that abnormal VOR gains do not necessarily indicate deficit in the semi-circular canals but in some cases, deficit elsewhere along the VOR pathway; that is what the vHIT records.

Summary points

- We found a statistically significant dependence of the six-canal vHIT VOR in patients with VS (vestibular schwannoma; retrolabyrinthine cause) between all ipsilateral canal gains
- On the other hand, such dependence was not observed in patients with superior semi-circular canal dehiscence (labyrinthine cause)
- Our observed correlations of VOR gains in patients with retrolabyrinthine disease could indicate a retrolabyrinthine origin of the vHIT responses.
- Abnormal vHIT gains might not necessarily indicate deficit of the semi-circular canal function only, rather a deficit along the VOR pathway; these findings enhance our understanding of vHIT gain origins.

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Table 1: Basic demographic information

	Total (n=40)	VS (n=20)	SSCD (n=20)	p-value
Age	50.7 ± 13.8	58.2 ± 13.9	43.2 ± 9.0	<0.001 (<i>t</i>)
Sex				0.752 (χ^2)
Female	19 (47.5%)	9 (45.0%)	10 (50.0%)	
Male	21 (52.5%)	11 (55.0%)	10 (50.0%)	
Pathological side				0.752 (χ^2)
Left	19 (47.5%)	10 (50.0%)	9 (45.0%)	
Right	21 (52.5%)	10 (50.0%)	11 (55.0%)	

VS: vestibular schwannoma, SSCD superior semi-circular canal dehiscence

Table 2: vHIT Gains Analysis

	Total (n=40)	VS (n=20)	SSCD (n=20)	p-value
SSC Pathological Status				0.197 (χ^2)
Abnormal	16 (40.0%)	10 (50%)	6 (30%)	
Normal	24 (60.0%)	10 (50%)	14 (70%)	
SSC vHIT Gains				
Normal Side	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.561 (t)
Ipsilesional Side	0.8 ± 0.2	0.8 ± 0.3	0.9 ± 0.2	0.126 (t)
LSC Pathological Status				0.014 (f)
Abnormal	12 (30.0%)	10 (50%)	2 (10%)	
Normal	28 (70.0%)	10 (50%)	18 (90%)	
LSC vHIT Gains				
Normal Side	0.9 ± 0.1	0.9 ± 0.2	1.0 ± 0.1	0.045 (t)
Ipsilesional Side	0.87 [0.24]	0.765 [0.537]	0.895 [0.085]	0.02 (w)
PSC Pathological Status				0.002 (χ^2)
Abnormal	20 (50%)	15 (75%)	5 (25%)	
Normal	20 (50%)	5 (25%)	15 (75%)	
PSC vHIT Gains				
Normal Side	0.855 [0.185]	0.835 [0.188]	0.880 [0.158]	0.22 (w)
Ipsilesional Side	0.785 [0.335]	0.550 [0.273]	0.875 [0.130]	<0.01 (w)

VS: vestibular schwannoma, SSCD superior semi-circular canal dehiscence, SCC: superior SC, LSC: lateral SC, PSC: posterior SC

Table 3: Correlation Of Ipsilateral Vhit Gains Based On Pathology

VS	Kendall Tau-B	p-value
Sup - Lat	0.549	<i><0.001</i>
Sup - Post	0.413	<i>0.012</i>
Lat - Post	0.578	<i><0.001</i>
SSCD	Kendall Tau-B	p-value
Sup - Lat	-0.325	<i>0.047</i>
Sup - Post	0.128	0.435
Lat - Post	0.165	0.313

VS: vestibular schwannoma, SSCD superior semi-circular canal dehiscence, [Sup: superior, Lat: lateral,

Post: posterior (always referring to semi-circular canals)]

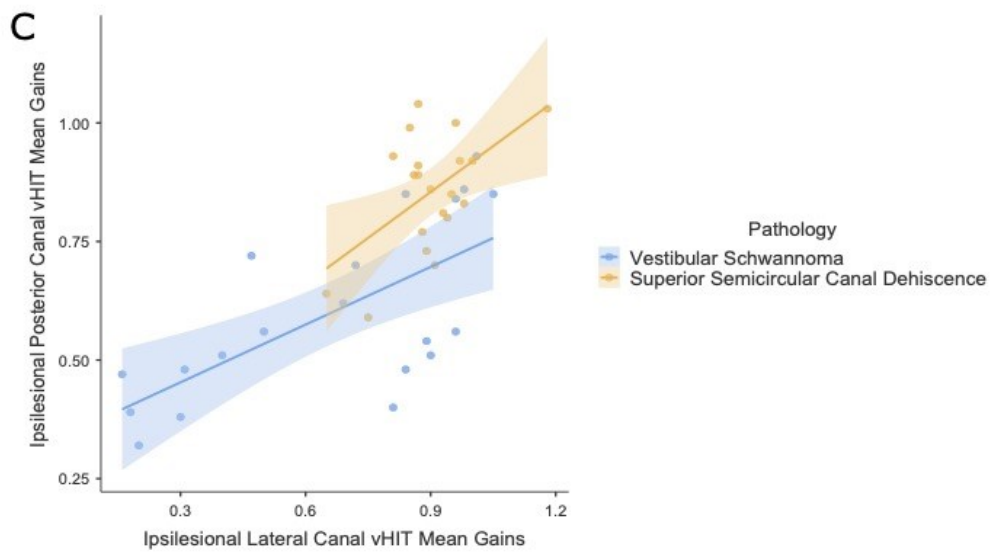
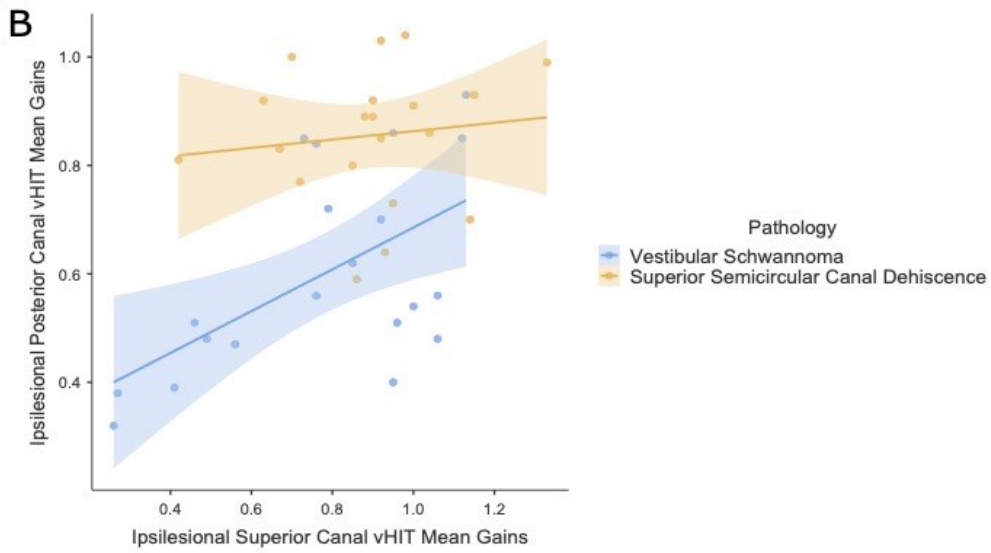
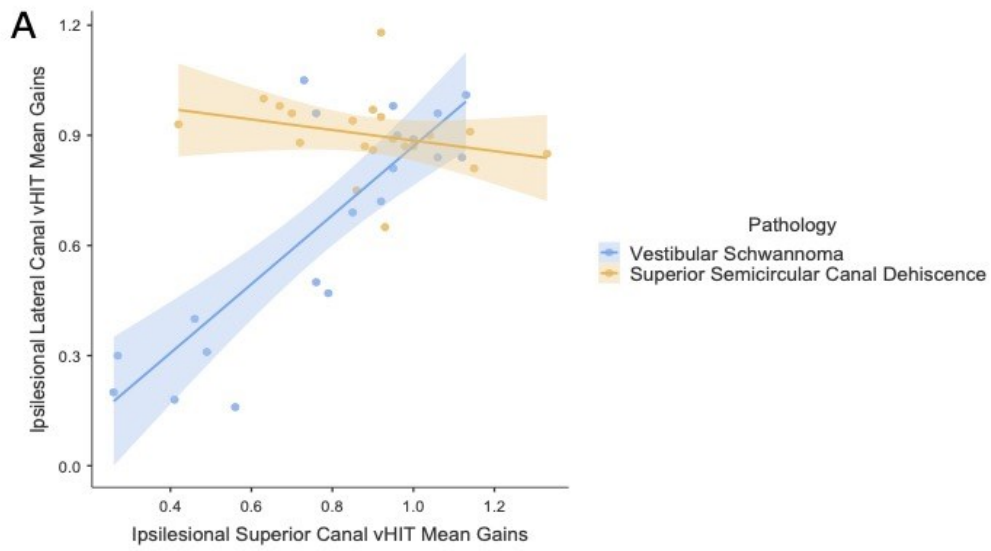


Figure 1: The correlations between the vHIT gains between the ipsilateral semi-circular canals in patients with VS and SSCD (A: lateral and superior canal, B: posterior and superior canal, C: posterior and lateral canal)