Innovative vestibular testing: applications in the pediatric environment, in the operating room, and in rehabilitation

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Contents

Abstract

Dizziness and vertigo are common complaints in the general population, affecting yearly 15-20% of adults and 5-25% of children of school age and having considerable impact on everyday life. As the assessment of peripheral vestibular deficits is challenging, it is crucial to dispose of techniques to provide clinicians support for the correct diagnosis.

The aim of this dissertation is therefore to apply in the clinical context cutting-edge diagnostic tools for the easy, quick and reliable assessment of peripheral vestibular impairments and the related functionality.

Traditional techniques for the evaluation of semicircular canals, such as the caloric test, the rotational test or the search-coil Head Impulse Test, present several disadvantages, being unpleasant, expensive, time-consuming, not always available at the bedside or appropriate for any group of patients. Additionally, testing the vestibular system at low frequencies, such as in the caloric test, does not cover the physiologically relevant range. The video Head Impulse Test (vHIT) represents an alternative to indirectly evaluate semicircular canals' function, stimulating the vestibulo-ocular reflex (VOR) with high-frequency head rotations and measuring the resulting eye and head movements. The first study reported in this dissertation extends the potentiality of the vHIT, assessing its feasibility in a group of healthy children and validating its use as a simple and well-tolerated bedside test for the vestibular screening of the pediatric population.

The quantitative outcomes of the vHIT, however, do not always reflect functionality, i.e., how efficient is the VOR in stabilizing the visual scene during head perturbations. This represents the starting point for the development of tests whose aim is to assess the subjective perception of this ability. Among the most recently introduced techniques, the Head

Impulse Testing Device (HITD) quantifies, without recording eye movements, patient's reading abilities while performing high-frequency passive head rotations during equally challenging visual stimuli. The second section introduces and validates a new diagnostic tool, the Head Impulse Testing Device-Functional Testing (HITD-FT), which combines the HITD with eye movements recording. The HITD-FT is tested on healthy participants, whose vestibular functionality is transiently impaired by opioid administration. The work assesses the combined effect of VOR and re-fixation saccades on gaze stabilization during high-frequency passive head rotations. Moreover, it describes the role of covert re-fixation saccades on image stabilization and in enhancing overall dynamic vision. The HIDT-FT is furthermore exploited within the context of this dissertation to monitor the overall dynamic visual performance of vestibular patients during rehabilitation.

The same experimental set-up, with healthy subjects undergoing opioid administration, is lately also exploited to explore the causes underlying post-operative nausea and vomiting, whose mechanism is still not completely understood. Preliminary studies suggest that opioids, acting on semicircular canals, generate a mismatch between the altered canals' inputs and other non-consistently altered sensory inputs, triggering nausea and vomiting. The here reported study investigates whether the mismatch between semicircular canals' inputs and other vestibular sensory inputs, or the mismatch between vestibular and visual inputs, are clinically relevant. A better understanding of this mechanism, i.e. that intra-vestibular mismatches have a particular importance, can help reducing the unpleasant side effects and improve pain management with opioids.

Zusammenfassung

Schwindelsyndrome sind häufig. Sie betreffen jährlich 15-20% der Erwachsenen und 5-25% der Schulkinder und haben erhebliche Auswirkungen auf den Alltag. Die Beurteilung peripherer vestibulärer Defizite ist eine Herausforderung. Daher ist es entscheidend, Methoden zur Verfügung zu haben um Mediziner bei der Diagnosestellung zu unterstützen.
Ziel dieser Doktorarbeit ist es, innovative Diagnose-Tools zur einfachen, schnellen und zuverlässigen Beurteilung der Funktion des vestibulären Systems in die Klinik zu übertragen. Traditionelle Methoden zur Evaluation der Bogengänge wie Kalorik, Drehstuhltest oder der Search-Coil-Kopfimpulstest haben mehrere Nachteile: sie sind unangenehm, teuer, zeitaufwändig, nicht am Krankenbett verfügbar oder eignen sich nicht für jede Patientengruppe. Die Untersuchung des vestibulären Systems im Niederfrequenzbereich wie bei der Kalorik deckt zudem nicht den physiologisch relevanten Bereich ab. Der videobasierte Kopfimpuls-Test (vHIT) ist dafür eine Alternative. Durch Stimulation des vestibulo-okulären Reflexes (VOR) mit Hochfrequenz-Kopfdrehungen und Messung von Auge- und Kopfbewegung wird dabei indirekt die Funktion der Bogengänge untersucht. Die erste Studie dieser Doktorarbeit erweitert die Anwendung des vHITs; seine Durchführbarkeit wird bei gesunden Kindern geprüft. Er stellt sich als einfacher und gut verträglicher „Bedside Test“ für das vestibuläre Screening bei Kindern heraus.
Die quantitativen vHIT Ergebnisse alleine spiegeln nicht immer wider, wie gut das Sehen während Kopfbewegung stabil gehalten wird. Dies war Ausgangspunkt für die Entwicklung von Tests zur subjektiven Wahrnehmung dieser Funktion. Eine neue Methode auf diesem Gebiet, der Head Impulse Testing Device (HITD), untersucht - ohne Messung der Augenbewegungen - die Lesefähigkeit anspruchsvoller visueller Stimuli während

passiven Hochfrequenz-Kopfimpulsen. Im zweiten Teil der Doktorarbeit wird ein innovatives Diagnose-Tool – Head Impulse Testing Device – Functional Testing (HIDT-FT) – eingeführt und validiert. Der Test kombiniert HIDT mit Augenbewegungsmessung. Der HITD-FT wird an gesunden Probanden geprüft, deren vestibuläre Funktion mit Opioiden vorübergehend beeinträchtig ist. Die Studie untersucht den kombinierten Effekt von VOR und Re-Fixationsakkaden auf die Blickstabilisierung während passiver Hochfrequenz-Kopfimpulsen. Außerdem wird die Rolle sogenannter verdeckter (covert) Re-Fixationsakkaden bei der Bildstabilisierung und beim dynamischen Sehen geprüft. Der HITD-FT wird im Rahmen der Doktorarbeit zudem erfolgreich zur Dokumentation des dynamischen Sehens bei der Rehabilitation vestibulärer Patienten eingesetzt.

Zum Schluss wird ein ähnlicher Versuchsaufbau mit Gabe von Opioiden bei Gesunden benutzt, um der Ursache von postoperativer Übelkeit und Erbrechen näher zu kommen, deren Mechanismus bisher nicht gut verstanden ist. Vorarbeiten legen nahe, dass Opiate eine Wirkung auf die Bogengänge haben und dass so eine Inkongruenz zwischen geänderten Bogengangs-Eingängen und nicht konsistenten geänderten anderen sensorische Inputs entsteht, die zu Übelkeit und Erbrechen führt. Die hier vorgelegte Arbeit untersucht, ob die Inkongruenz zwischen Bogengangsinformation und anderen vestibulären Sensoren oder die zwischen vestibulärem und visuellem Eingang klinisch relevant ist. Das Verständnis, dass intra-vestibuläre Inkongruenzen vor allem von Bedeutung sind, kann helfen diese unangenehmen Nebenwirkungen zu reduzieren und die Schmerzbehandlung mit Opiate zu verbessern.

Chapter 1

Introduction

Vertigo and dizziness are cardinal symptoms of vestibular disorders. Often associated with vegetative symptoms, they are among the most common complaints in medicine, affecting approximately 15-20% of the adult population [1] and 5-25% of children of school age [2–4] per year. They are one of the most frequent causes of emergency department visits [5]. Vertigo and dizziness have a considerable impact on everyday life, limiting social activities and correlating with anxiety and depression (for review see [6]). However, the correct diagnosis of vestibular dysfunctions is often challenging, as the patient's report of vestibular symptoms is highly subjective and as dizziness and vertigo can be the expression of different underlying pathological conditions. The assessment of patients complaining about vertigo and dizziness is usually performed complementing patients' history with vestibular instrumental examinations. The availability of reliable testing techniques, quick and exploitable at the bedside, is therefore crucial to provide clinicians support for the correct and prompt diagnosis of vestibular impairment.

The vestibular system is responsible for the sense of balance, providing, together with vision and proprioception, information about self-motion and self-orientation, and about the position of the body in relation to the environment. In the peripheral vestibular system, situated inside each inner ear, two main structures can be distinguished: three semicircular canals (anterior, posterior and horizontal), associated to the three extra-ocular muscles, and two otolith organs, utricle and saccule. The semicircular canals are sensitive to the three components of head angular acceleration, while the otolith organs sense linear acceleration and gravity [7].

To investigate the correct functionality of the peripheral vestibular structures, medical doctors can choose among different instrumental examinations. Traditional vestibular tests for the evaluation of semicircular canals' function are the caloric test and the rotational test.

The caloric test, introduced by Robert Bárány [8], consists of bithermal irrigation of each ear canal with warm (44°) and cold (30°) air or water, in order to elicit vestibular nystagmus, thus involuntary rhythmic eye movements. It corresponds to a single, very low frequency (0.003 Hz) vestibular stimulation [9]. The response, i.e. the maximum velocity of the slow-phase of nystagmus, determines if there is a significant asymmetry between the two sides (quantified with the Jongkees formula [10]). The caloric test reliably detects unilateral vestibular dysfunctions but it is less appropriate in case of bilateral deficit. Moreover, it is less applicable in case of partial occlusion of the ear canal, where a reduced response may be caused by inadequate irrigation [11]. The stimulation can elicit nausea and dizziness, and may lead to tympanic membrane perforation or external otitis [12]. The caloric test is not available at the bedside, and takes approximately 30 minutes to be completed.

As an alternative, rotational testing is performed. Here, whole-body rotations are applied while the subject sits on a rotating chair and compensatory movements of the eyes with respect to the head rotation are analyzed. Test execution lasts approximately 45 minutes to one hour. As the stimuli are computerized, they can be precisely applied and different frequencies can be tested. As the rotations affect both ears simultaneously, the rotating test is useful to determine the presence of a bilateral impairment but it is less reliable in case of unilateral vestibular deficit [11, 13]. Moreover, rotational chairs are expensive and require an appropriate setting, only available in some specialized structures. As described, none of the considered techniques for the evaluation of semicircular canal are easy to apply, quick and mobile.

In 1988, Halmagyi and Curthoys introduced the Head Impulse Test (HIT), or Head Thrust Test, the first clinical bedside test for the assessment of semicircular canal function [14], exploiting the mechanisms driving the vestibulo-ocular reflex. The vestibulo-ocular reflex (VOR) is the reflex that triggers compensatory eye movements in response to head perturbations, especially during locomotion, to maintain clear vision by stabilizing the image of a stationary object on the retina. The VOR can respond both to the rotational component of the head movements (angular VOR, mediated by the semicircular canals) and to the linear component (translational VOR, mediated by the otolith organs) [7,15]. Throughout this dissertation, the term VOR refers to the angular vestibulo-ocular reflex. Other visually mediated mechanisms, such as the optokinetic reflex and smooth pursuit, cooperate in stabilizing images on the retina, but only the VOR is fast enough to promptly react to natural head movements [7]. In case of a lesion, after the acute phase, the vestibular system adapts to the new pathological condition and relies on the available visually mediated mechanisms to stabilize gaze; these compensatory mechanisms are particularly effective in stabilizing the visual scene at low frequencies. Vestibular stimulation applied during caloric or rotational tests ($<$1 Hz) is then inadequate in detecting vestibular deficits. On the other hand, in case of abrupt, high-frequency ($>$1.5 Hz), unpredictable head movements as applied in HIT, visually mediated mechanisms are too slow, and therefore ineffective, to compensate for the deficient VOR; to stabilize gaze, subjects have to trigger re-fixation saccades, unveiling consequently the VOR impairment [7, 14]. Stimuli characterized by high-frequency components are moreover physiologically similar to movements performed during everyday activities [16], such as walking [17]. It is therefore behaviorally relevant to assess the VOR in this particular frequency range. For these reasons, challenging the VOR at high frequencies is the most reliable way to indirectly evaluate semicircular canals' function. The HIT consists of applying passive head rotations to the left and the right in the plane of a pair of semicircular canals while the subject is instructed to fixate a target at eye level, and to observe the resulting eye movements. The standard evaluation is usually limited to the horizontal semicircular canals, as the responses are easily and reliably determined [11], even if vertical semicircular canals function can also be tested [18]. The applied head rotations are unpredictable in time and direction, in order to prevent anticipatory movements, and characterized by high-acceleration (2000-7000$^\circ/s^2$) and small-amplitude

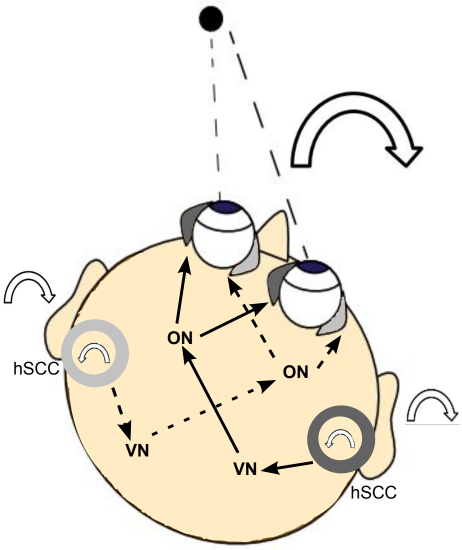

Figure 1.1: Simplified neural mechanism for horizontal vestibulo-ocular reflex (VOR). The horizontal semicircular canals (hSCC) on both sides detect a head rotation to the right and trigger the VOR. They send impulses through the vestibular nerve to the vestibular nuclei (VN), which project to the contralateral oculomotor nuclei (ON). While one side is excited (dark grey, solid lines), the other is inhibited (light grey, dashed lines). The oculomotor nuclei drive eye muscle activity via the oculomotor nerve. As a result, the eyes move to the opposite direction of the detected head rotation.

(10°-20°). The tested frequencies are in the range 5-7 Hz, physiologically corresponding to head movements performed during everyday activities [16, 19]. In the physiologically intact VOR, as soon as the vestibular organs detect the head rotation towards one direction, from the vestibular nuclei excitatory signals are sent to the oculomotor nuclei to stimulate the corresponding extra-ocular muscles, generating a perfect compensatory rotation of the eyes towards the opposite direction of the detected head movement (for a schematic representation, see **Figure 1.1**). Gaze is stable on the designed target [7, 20] (**Figure 1.2, panel A**). If the VOR is impaired, the eyes move partially in the same direction of the head during the rotation, forcing the patient to generate a re-fixation saccade, i.e., a quick eye movement that brings the eyes closer to the target. In this case, both the residual VOR and the re-fixation saccades act synergistically to stabilize gaze [7] (**Figure 1.2, panel B**). Re-fixation saccades can occur either while the head is still rotating, therefore

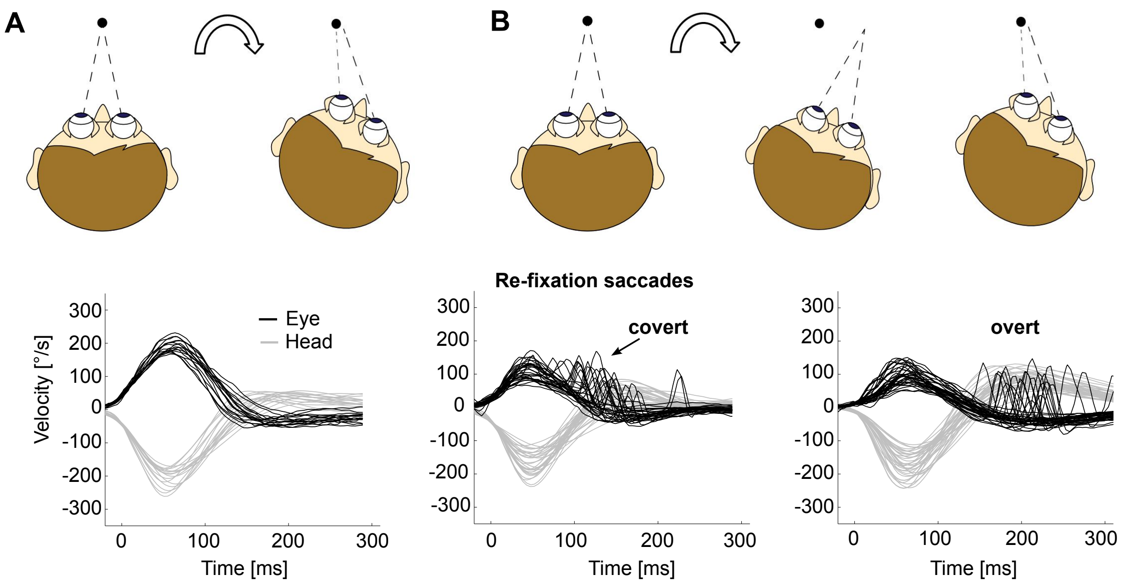

Figure 1.2: Intact and impaired vestibulo-ocular reflex (VOR).
A) When the head is rotated towards one direction, the intact VOR drives a perfect compensatory rotation of the eyes towards the opposite direction. Gaze is stable on the designed target. Eye movements perfectly mirror head movements (below).
B) If the VOR is impaired, the eyes move partially in the same direction of the head during the rotation, forcing the patient to generate a re-fixation saccade to bring the eyes back on target. Re-fixation saccades (below) can occur during the head movement (covert saccades), or after it (overt saccades).

with a shorter latency (covert saccades [21]) or only after the head movement (overt saccades), and are considered an indirect sign of impaired semicircular canal function, with re-fixation saccades present with head rotations to the side of the lesion. Only overt, not covert, re-fixation saccades are visible to the naked eye [21]. As covert saccades cannot be detected in the clinical examination, they lead to false negative results; as a result, vestibular dysfunction is missed. With the clinical HIT it is thus possible to identify and lateralize the presence of a vestibular impairment, but not to provide an objective measure of VOR function or of the characteristics of the corrective saccades, whose evaluation depends on the subjective visual observation of the clinician [22].

Vestibular tests measuring simultaneously eye and head movements during HIT aim to overcome this limit. After first attempts in documenting the presence of re-fixation saccades during HIT using electronystagmography [23], the search-coil in magnetic-field recording technique became the gold standard for recording eye and head movements [20] while performing HIT. This method allows both to quantify the VOR deficit and to unveil the presence of re-fixation saccades [20, 21, 24–26]. The search-coil technique has however the disadvantage of requiring the subject to wear an uncomfortable special contact lens during the test upon administration of topical anesthetics, and is time-consuming, expensive and not recommended for acute patients [22]. Also, it is not suitable for a bedside examination [27]. A valid and more comfortable alternative is represented by the videooculography (VOG), that allows the recording of eye movements in three dimensions by detection of the pupil through an infrared camera mounted on dedicated goggles, combined with inertial sensors to record head motion. The use of VOG while performing HIT is referred to as video Head Impulse Test, or vHIT. The vHIT allows the vestibular testing by monitoring eye movements through a high-speed video camera and simultaneously sensing head movements through inertial sensors [22]. The VOR performance is quantitatively evaluated calculating the gain, computed as the ratio between eye and head velocities during a given period of time after the onset of the head rotation, and phase shift, the offset in the timing of eye movement relative to head motion. A gain of one and a phase shift of 180° indicate intact VOR function. As VOR gain is permanently reduced in response to impulses toward the impaired side, a gain value below 0.79 is considered sign of a deficient VOR on that side ([19] and in analogy to [28]). In addition to gain, it is also possible to identify covert and overt re-fixation saccades, analyzing each side separately [19]. vHIT performances about the reliable detection of semicircular canals' dysfunctions and about the estimation of the VOR gain are comparable to those of the search coil technique [22,29,30], avoiding however the related discomfort. The system is easy to use and provides immediate results via the automated analysis software [22]. The examination is quick (approximately 5-10 minutes), and non-invasive. The light equipment allows also the testing at the bedside [19]. vHIT is an innovative and new technique, whose application in the clinical context has only recently spread. Still few years ago, there was only limited experience in the validation of vHIT in healthy adults [27], in older individuals [29] and in vestibular patients [19]. Recently, it has been exploited also in the clinical set-up to discriminate between central and peripheral deficits [31] and to characterize compensatory saccades in patients after cochlear implant surgery [32] and covert anti-compensatory quick-eye movements (CAQEM) in vestibular patients [33]. There was however no experience in performing vHIT in difficult clinical situations. The main goal of the works reported in this dissertation is therefore to adapt this well suited system to be exploited in critical patients' populations or challenging clinical settings, and, additionally, to deepen the understanding of the peripheral vestibular system.

The first study included in this dissertation (**Chapter 2**, [34]) translates the use of the vHIT to the pediatric population. Children and adolescents represent a critical and often neglected subgroup of patients, although vestibular related disorders are common not only among adults, but also in childhood. According to epidemiological studies the yearly prevalence of vertigo and dizziness in children of school age is 5-25% [2–4], often associated with other disturbances, such as migraine-equivalents [35,36]. A fully functional vestibular system plays a fundamental role, together with the visual system and proprioception, for the development of balance and gross motor function in children [37]; missed vestibular deficiency in childhood can therefore have serious and significant repercussions in adulthood [11]. Congenital or acquired vestibular dysfunction may indeed lead to impaired motor development (delays in the acquisition of head control, sitting and independent walking compared to healthy children of the same age [38–43] and inadequate postural control [37]). Children with vestibular problems represent also a significant part of the population with learning problems [44]: vestibular deficit can affect cognitive development, leading to inattentiveness, limited concentration and avoiding behaviors, often associated with psychiatric problems [43]. Due to the close connection between vestibular and visual system, a vestibular deficit may also compromise eye motor control, interfering with the alternation of saccadic movements and fixations required for reading [45], impairing visual acuity and, consequently, reading acuity [46]. The correct identification of a vestibular deficit at early stages is crucial for a prompt and adequate motor intervention plan; early vestibular rehabilitation, teaching children how to substitute the missing vestibular function with other sensor and motor strategies, could prevent or reduce later problems [40]. In childhood, the diagnosis of the main symptoms of balance disorders or vestibular problems is often not clear, because of the lack of standard specific tests for this age group [11] and as the spectrum of the diagnosis is different than in adults [47]. Children are moreover inexperienced in reporting vestibular complaints and inaccurate in describing how long a vertigo attack lasts or which are the coexisting symptoms [48]. In addition to that, they do not report the often concurrently related visual disturbances, as they are not aware of the underlying problem [40]. Vestibular investigation techniques described for adults are applied to children as well [11]. Children are nevertheless more likely prone to fear and bad tolerate vestibular testing, because of the unpleasant enhanced vertigo and nausea, or to be inattentive, leading to test termination before completing the evaluation. The caloric test has been performed in very young children, but the elicited vertiginous sensation caused by ears irrigation is often frightening [12,13,49], impairing the execution of the examination in up to 25% of the tested children [12]. The duration of about 30 minutes represents also a limit in the feasibility of the test in small children. The rotational chair could be considered as an alternative, even though also this test requires too long to keep children attention [13] and should therefore sometimes been shortened [11]. Additionally, children younger than 3 years old cannot sit on the chair on their own, becoming agitated, often causing procedure termination [13]. The search-coil technique for eye movements recording, moreover, being invasive, is also not well tolerated. To summarize, while the early screening of the normal vestibular function becomes decisive in reassuring children and parents about the normal vestibular function, it is essential to avoid invasive and bad-tolerated investigations. The introduction of an easy and quick vestibular test optimized to meet children's needs would be necessary. The first described study assesses feasibility and tolerance of vHIT in healthy children and adolescents. As outcome measures, normative VOR gain values for the different age groups, as well as the presence of re-fixation saccades and of CAQEM are reported.

vHIT nicely provides quantitative information about VOR gain and re-fixation saccades behavior. However, these indicators do not always fully reflect the functionality of the vestibular system, i.e. its efficacy in stabilizing the visual scene, and, as a consequence, the subjective perception of disability. The second publication reported in the dissertation (**Chapter 3**, [50]) will then be focused on the assessment of vestibular functionality. As previously illustrated, the main goal of the VOR is to stabilize images on the retina in spite of head perturbation, thus to allow clear vision also during activities as walking, where each step causes the image to be displaced on the retina [51]. If this mechanism is compromised, causing retinal slippage of even few degrees per second [52, 53] the vision is deteriorated. This impairment is especially relevant in patients affected by bilateral vestibulopathy, where the VOR is unable to compensate for head movements during everyday movements [51, 54]. They complain indeed of oscillopsia [55], thus the illusionary sensation of motion of stationary objects during head movement, which leads to visual difficulties, accompanied by the sensation of disequilibrium and postural instability [54]. The visual discomfort is caused by a decrease in dynamic visual acuity (DVA), defined as visual resolution during head perturbation with respect to the static condition, due to the inefficient VOR compensation. Poor DVA, perceived as blurred vision, reduces the ability of detecting details, for example while reading during motion [51], interfering with daily activities, and, as a consequence, affecting negatively their quality of life [51,54]. These observations represent the starting point for the development of techniques whose aim is the assessment of the peripheral vestibular system from a functional perspective, to investigate how efficient is the VOR in gaze stabilization during head rotations, avoiding eye movements recording. The first attempt was done assessing VOR during head rotations while looking at a stationary visual target [56]. Several protocols were successively tested in this direction, measuring subjects' DVA, both exploiting active [57,58] and passive [59,60] head movements and different types of visual stimuli [60, 61]. Passive head movements, following the rationale of the HIT, are however more informative in the detection of a vestibular dysfunction, as compensatory strategies such as adaptation (based on residual vestibular inputs) and/or substitution (by vision or proprioception) are not available [62, 63]. Computerized techniques represented a step forward in the optimization of the method, as the selected visual stimulus could be synchronized with head velocity [57, 58, 64]. The test has been further improved by selecting as visual stimuli Landolt rings in eight possible orientations and using an adaptive algorithm [65] to determine the DVA threshold [66]. The explored techniques demonstrate that the DVA performance reflects VOR functionality and it is a valid indicator of vestibular deficits, even though it does not always correlates with the subjective perception of disability. Ramat et al. recently developed a new computerized technique, the Head Impulse Testing Device (HITD [67,68]), whose aim is to assess the peripheral vestibular function exploiting passive high-frequency (2000-6000$^{\circ}/s^2$) head rotations in spite of equally challenging visual stimuli. The test, focused on head movements' characteristics, does not involve eye movements' measurement. Such a tool is important to assess patients' subjective percept of impairment. Technical improvements to the HITD were lately introduced [69], developing a new diagnostic tool, the Head Impulse Testing Device- Functional Test (HITD-FT). The HIDT-FT combines the quantitative testing of the VOR, performed through vHIT and the vestibular functional HITD [68]. It allows the simultaneous recording of head and eye movements during HIT and to monitor display timing of the visual stimuli and their temporal synchronization with the head movements during DVA test. With a diagnostic tool that combines HITD with eye movements recording, it is now possible, besides the quantitative and functional testing of the VOR, also to assess the saccade behavior. In particular, it is possible to better understand the consequences of triggering re-fixation saccades on image stabilization. As previously described, if the VOR is impaired, some bilateral vestibular patients can trigger re-fixation saccades during (covert saccades), or after (overt saccades), head movements [21]. The functional implication of triggering covert re-fixation saccades has however never been investigated. It has been hypothesized that short-latency re-fixation saccades, moving the eyes as quickly as possible back on the target, could be beneficial in improving gaze stabilization, hence reducing oscillopsia and facilitating reading in DVA tests.

Here, in analogy to the approach of Colagiorgio et al. [69], the HIDT-FT has been adapted to assess vestibular functionality in a challenging clinical context. The first aim of the study was to validate the HIDT-FT as a useful tool to assess the synergic effect of VOR and re-fixation saccades during high-acceleration head rotations; secondarily, to investigate the function of covert saccades in stabilizing gaze and in enhancing dynamic vision. In doing that, a model of acute bilateral vestibular dysfunction was exploited; to transiently and reversibly reduce VOR gain in healthy subjects the opioid remifentanil was administred. It is indeed well-know that opioids affect the vestibular function [70–72]. Among them, remifentanil was chosen as, besides side effects as nausea, vomiting, itching, and difficulties in swallowing and in fixating, it also transiently affects the functionality of the vestibular system by inducing down-beat nystagmus and by decreasing VOR gain [73].

The perioperative experimental setting and the opioid remifentanil were then lately exploited to address another critical question (**Chapter 4**, [74]), i.e. to investigate the mechanisms of opioid-induced nausea and vomiting (OINV), one of the main reasons for post-operative nausea and vomiting (PONV) [75, 76]. Opioids such as remifentanil play a fundamental role in in pain management, but their side effects have a negative impact on patient satisfaction [77] and on healthcare costs [78]. In particular, opioids' triggering effect on nausea and vomiting is still not completely understood. It has been suggested that they have a direct effect on the emetic center in the brainstem [79] and that they affect the vestibular function [70–72], being opioid receptors present in both the peripheral [80] and central vestibular structures [81], and thus mediating changes in the VOR response. It has been recently shown that remifentanil compromises semicircular canals' function, decreasing temporarily and reversibly horizontal VOR gain, assessed through the vHIT [50, 73]; movement enhances nausea during its administration, while resting reduces it [73,82]. One possible explanation of this mechanism could be the mismatch between the impaired semicircular canals input and other sensory inputs during head motion [73,82]. A similar mismatch would be also the reason of motion sickness [83,84], where the information coming from vision, vestibular and proprioceptive inputs are in conflict one with another, and hence with what is expected. This discrepancy is emetogenic, with effect proportional to the extent of the discrepancy and to the number of conflicting sensory inputs involved in the mismatch [83]. The sensory discordance could be however attributed both to an intersensory mismatch, with vision or proprioception, or to an intra-vestibular one, caused by the conflict between the altered semicircular canal's input and the non congruent otoliths' information [83], as happens in space motion sickness [85]. The reported study wants to provide a deeper understanding of the mismatch mechanism, in particular considering the role of vision as a trigger for these unpleasant side effects. Outcomes will be beneficial in pain management with opioids.

1.1 Aim of the dissertation

The aim of this dissertation is to apply innovative vestibular function tests, i.e., the video Head Impulse Test (vHIT) and the Head Impulse Testing Device – Functional Testing (HITD-FT) in challenging clinical settings, translating these recently developed techniques into clinical practice.

The final goal is to improve vestibular testing focused on the assessment of semicircular canals' function and to establish cutting-edge methods to both identify vestibular disorders and evaluate the functional performance of the VOR. The vHIT and HITD-FT were adjusted for use in critical groups, such as the pediatric population or patients with bilateral vestibulopathy, and in critical settings as the operating room. Exploiting the same experimental setting, it was also possible to better understand the interaction between the vestibular system and the opioid remifentanil, providing relevant findings in the pain management with opioids.

In the first publication, the use of vHIT has been translated to the pediatric population. vHIT was validated in children and adolescents and normative VOR gain data for the considered age groups were provided.

The second section shows how the HITD-FT can be exploited as a new diagnostic tool to assess the combined effect of VOR and covert re-fixation saccades on overall gaze stabilization, and to investigate the role of covert re-fixation saccades on dynamic vision. For this purpose, an opioid model of vestibular dysfunction was used.

The same opioid, remifentanil, has been used in the third publication as a model to explore the mechanisms causing OINV, focusing in particular on the role of vision.

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Chapter 2

Clinical and video head impulses: a simple bedside test in children

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Chapter 3

The Effect of Vestibulo-Ocular Reflex Deficits and Covert Saccades on Dynamic Vision in Opioid-Induced Vestibular Dysfunction

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Chapter 4

Preventing Opioid-induced Nausea and Vomiting: Rest Your Head and Close Your Eyes?

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Chapter 5

Discussion

This dissertation illustrates how recent and innovative diagnostic tools for peripheral vestibular testing are translated into clinical practice and how they are applied in challenging clinical settings. In addition, these techniques have been exploited to deepen the understanding of relevant issues about the physiology of the vestibular system, such as the functional role of covert re-fixation saccades and the influence of opioids on the vestibular system.

The aim of the first publication is to adjust the vHIT for use in the pediatric population and to assess its tolerance among children and adolescents. As dizziness and vertigo are common in childhood [1], early vestibular screening is extremely important to prevent motor and cognitive development delays [2, 3]. The accurate diagnosis of vestibular disorders can be even more challenging than in adults, because of their incapability of reporting symptoms and as traditional vestibular examinations, such as caloric or rotational tests, not optimized for testing children, are often bad tolerated [4]. In the reported study, the peripheral vestibular function is assessed with vHIT in 44 healthy children between 4 and 18 years of age. The outcomes considered are VOR gain, presence of re-fixation saccades and presence of CAQEM. As shown, vHIT nicely provides quantitative information about VOR gain and assesses the presence of saccades, indicators of vestibular impairment. Normative proposed VOR gain ranges for the different age groups are 0.79-1.08 (4-7 years old, early childhood), 0.85-1.06 (8-11 years old, middle childhood) and 0.86-1.06 (12-18 years old, late childhood). Being non-invasive, easy to perform and allowing a quick testing procedure (5-10 minutes), vHIT offers several advantages compared to traditional testing techniques. It provokes less distress and anxiety even in small children and it does not elicit vertigo or nausea as it could happen during caloric or rotational tests: none of the children that participated in the study reported any discomfort and all of them were able to complete the test without encountering any particular problem. To conclude, this study shows that the vHIT represents a valid alternative to traditional vestibular examinations in children and adolescents and it is a useful diagnostic screening test for complementing any assessment of vestibular developmental evaluation.

In the second proposed study, the newly developed HITD-FT has been introduced as a useful tool to document the combined effect of residual VOR and re-fixation saccades on dynamic visual acuity, evaluated as reading performance, during passive high-acceleration head rotations. The HITD-FT is tested on a group of fourteen healthy participants, whose vestibular functionality is pharmacologically impaired to obtain a model of acute vestibular failure. The bilateral vestibular deficit is transiently and reversibly induced using an opioid in a controlled perioperative environment. Remifentanil, a potent ultra-short-acting synthetic opioid analgesic drug, was chosen for his well-known pharmacokinetics [5]. The testing procedure is based on the approach of Colagiorgio et al. [6]. Participants are tested before and during remifentanil administration, and the considered outcomes are VOR gains and rate of correct answers in the functional test (HITD-FT score) in the two conditions. Results show that remifentanil does affect the peripeheral vestibular system, decreasing VOR gain and, as a consequence, also the ability of correctly recognizing the displayed visual stimuli. The HITD-FT nicely reflects this correlation, detecting both gain changes and reduced dynamic visual acuity (HITD-FT score). Moreover, the test also assesses the impact of covert saccades on the resulting visual performance, showing that covert re-fixation saccades, bringing quickly eyes back on the displayed visual stimulus, indeed reduce retinal slippage and improve dynamic vision. To summarize, the HITD-FT is an innovative and efficient method to document gaze stabilization and covert re-fixation saccades and to assess overall dynamic visual performances. In contrast with other DVA tests, it challenges the vestibular system with head movements close to everyday experience [7,8],

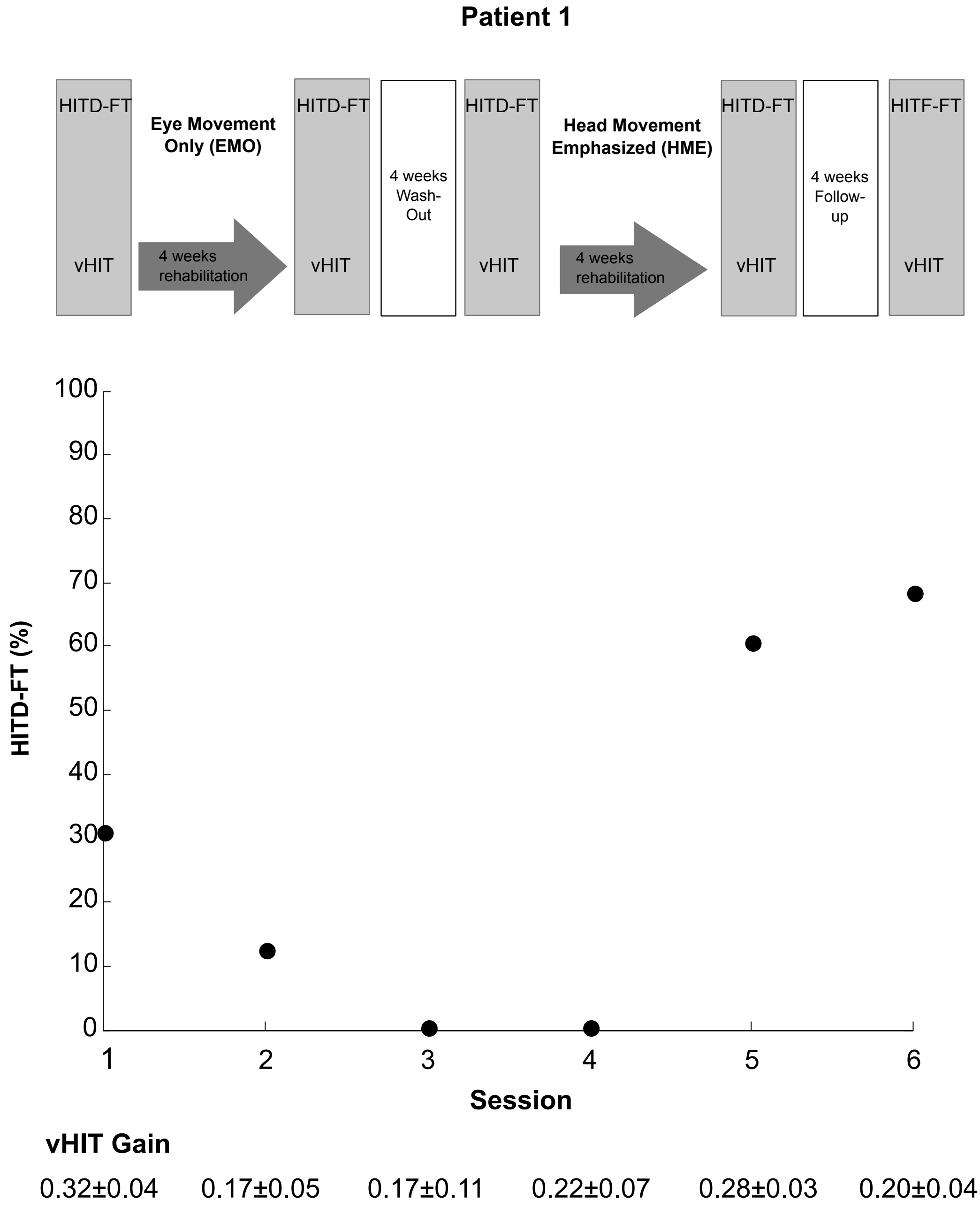
providing a direct measure of vestibular functionality, related to the subject's impairment in daily life.
In the third section, the opioid remifentanil is again exploited in the operating room to better understand the mechanisms causing opioid-induced nausea and vomiting (OINV), one of the main reasons behind post-operative nausea and vomiting (PONV) [9,10]. The study wants to disentangle the origin of this conflict, with focus on the relevance of visual input. In particular, the goal is to understand whether the visuo-vestibular mismatch is relevant in generating nausea and vomiting, validating the suggestion of closing the eyes, in addition to avoiding head movements. Fourteen healthy subjects experienced remifentanil infusion twice, once blindfolded and once with eyes open, with head and trunk passively moved during opioid administration. Motion-dependent nausea and vomiting are assessed before administration, 30 minutes after administration, and after subjects being moved. Findings show that vision is not the major responsible for OINV, being nausea during opioid administration triggered by movement and avoided by rest in all subjects, independently of visual input. This suggests that, more likely, the relevant trigger for the mismatch is an intra-sensory discordance between the differently altered semicircular canals and otoliths inputs. As previously shown [11], therefore, avoiding head movements is a good clinical practice to prevent or reduce OINV after transient opioid administration, while closing the eyes seems less relevant.

5.1 Further applications

As described, the HITD-FT provides information about patients' overall visual perception during head motion, thus the combined effect of VOR and re-fixation saccades. This more readily reflects everyday life's performances than the quantitative measure of the VOR gain alone. These properties make the HITD-FT a good tool to monitor the effect of vestibular rehabilitation, where overall dynamic visual performance matters, and to design rehabilitation programs accordingly. In the course of this dissertation, the HITD-FT has

been then further exploited in such a context; in particular, it was applied for the follow-up of patients affected by chronic bilateral vestibulopathy.
Chronic bilateral vestibulopathy, whose prevalence in the USA is 28/100.000 [12], lead to oscillopsia and postural instability and strongly impairs the quality of life of the affected patients [5, 12–14], increasing the risk of falls [12] and limiting their participation in social activities [12, 15]. The prognosis is bad, with almost no improvements over the years for more than the 80% of patients [16]. Vestibular rehabilitation is the only available treatment, with up to 60% of patients affected by vestibular disorders improving after physical therapy [17–19]. Evidence from eye-head control in vestibular impairment suggests that that head movement is a relevant aspect of vestibular rehabilitation [20, 21]. For this reason, an innovative head-movement based intervention was specifically designed for the treatment of chronic bilateral vestibulopathy. The aim of the study was to assess whether rehabilitation exercises based on emphasized head movements enhance subjective visual perception. Two chronic bilateral vestibular patients (men, 49 and 58 yeas old) were recruited at the Dizziness Center for Vertigo and Balance Disorders (DSGZ) of the Munich University Hospital. They were trained with two different rehabilitation programs of the duration of 4 weeks each, spaced out by 4 weeks of wash-out. One intervention was based on active Head Movement Emphasized (HME) rehabilitation, the second intervention on Eye Movement Only (EMO) rehabilitation. In a double-blind crossover design, the patients were randomly assigned to first undergo the EMO program and, after the wash-out, the HME (Patient 1, **Figure 5.1**), or vice-versa. Before and after each intervention and 4 weeks after terminating the second intervention (follow-up), their improvements were assessed through the HITD-FT. Patient 1 had an additional assessment 4 months after having completed both rehabilitation programs. As outcomes, HIDT-FT scores before and after HME rehabilitation were considered. Results show that HME treatment improved dynamic visual perception in both patients, with HITD-FT scores increasing for Patient 1 from 0% to 60% and for patient 2 from 0% to 75% (**Figure 5.1**).

The findings suggest that head movements are indeed relevant for vestibular rehabilitation, and that HME rehabilitation represents a promising approach in the treatment of


Patient 1
HITD-FT
Eye Movement Only (EMO)
4 weeks rehabilitation
vHIT
HITD-FT
vHIT
4 weeks Wash-Out
HITD-FT
vHIT
Head Movement Emphasized (HME)
4 weeks rehabilitation
HITD-FT
vHIT
4 weeks Follow-up
HITF-FT
vHIT
HITD-FT (%)
Session
vHIT Gain
0.32±0.04
0.17±0.05
0.17±0.11
0.22±0.07
0.28±0.03
0.20±0.04

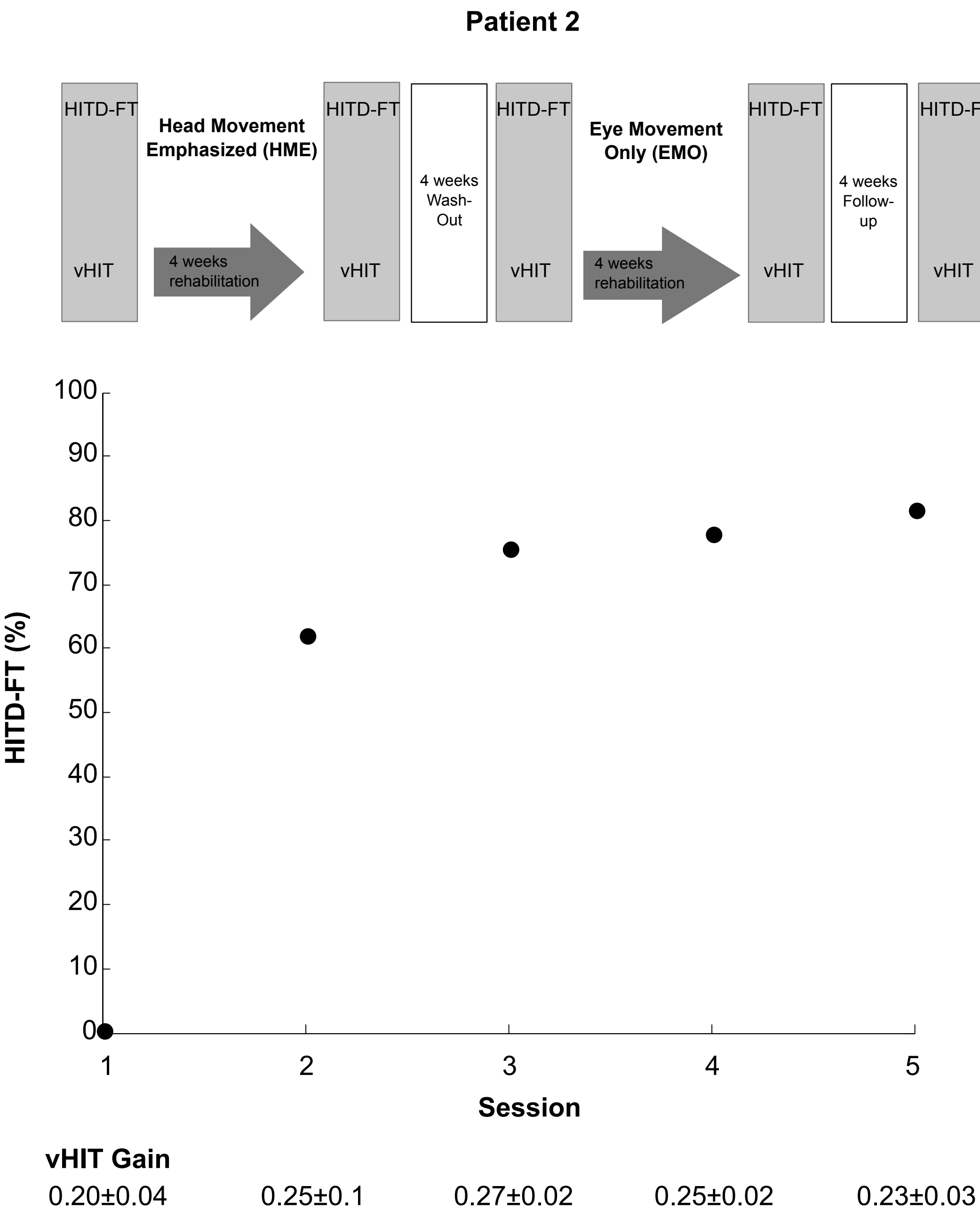


Figure 5.1: Head-movement emphasized (HME) rehabilitation in patients with chronic bilateral vestibulopathy. Intervention design, HIDT-FT scores (black dots) and vHIT gain for each session (Session 1-5) are shown. Patient 1 was trained with Eye Movement Only (EMO) rehabilitation first, followed by 4 weeks of wash-out, and then Head Movement Emphasized (HME) rehabilitation. He had an additional measurement (Session 6), about 4 months after terminating the program. In a crossover design, patient 2 underwent first HME, and then EMO rehabilitation. HITD-FT increased after HME rehabilitation for Patient 1 from 0% to 60%, and for Patient 2 from 0% to 75%. This result indicates a strong improvement in dynamic visual perception.

chronic bilateral vestibulopathy. These results have to be considered as part of a preliminary study; it is necessary to test the effect of the HME intervention on a larger cohort of patients and for a prolonged follow-up period, correlating HITD-FT scores with other neurophysiological measurements and participation and quality of life measures. With the outcomes provided by the HIDT-FT, it will also be possible to consider the contribution of VOR and re-fixations saccades, respectively, in the improvement following HME rehabilitation. However preliminary, this study demonstrates that HITD-FT is an appropriate tool also in the vestibular rehabilitation context, useful to easily assess visual perception during head motion before and after interventions.

5.2 Implications for future research

In summary, the findings reported in this dissertation show how the most recent diagnostic tools for peripheral vestibular testing, vHIT and HITD-FT, are adjusted to be exploited in challenging group of patients and in critical clinical settings. As demonstrated, the vHIT represents a cutting-edge diagnostic system to successfully assess the VOR also in the pediatric population. The HITD-FT is an innovative tool that combines the quantitative examination of the VOR together with the functional measurement of overall dynamic visual performance. It is suitable to be exploited also at the bedside in the operating room and in opioid-induced vestibular dysfunction. The final and combined goal is to provide clinicians easy, well-tolerated and reliable tools for the comprehensive peripheral vestibular evaluation and for the assessment of the VOR functionality in challenging clinical situations. The proposed works can inspire future clinical studies. Both the vHIT and the HIDT-FT have all the requisites to be extensively exploited for the screening and the characterization of vestibular patients. This allows planning early and appropriate interventions and to design rehabilitation strategies dedicated to acute and chronic vestibular patients. The combination of vHIT and HITD-FT can also be exploited to monitor patients from the acute phase throughout the recovery.

As shown, the proposed techniques vHIT and HITD-FT can additionally be exploited to deepen the understanding of the peripheral vestibular system. They help answering open questions about the physiology of the vestibular system and its interaction with other sensory inputs. In this dissertation two examples are reported. First, to investigate the role of covert re-fixation saccades on gaze stabilization and of saccades' behavior could be beneficial in training patients to trigger cover re-fixation saccades, helpful for dynamic vision. Second, a better comprehension of the effects of substances on the vestibular system, as reported in this particular case for opioids, could eventually help reducing the related side effects, improving the pain management with opioids and reducing post-operative nausea and vomiting.

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List of abbreviations

CAQEM	covert anti-compensatory quick eye movements
DVA	dynamic visual acuity
EMO	eye movement only
HIT	head impulse test
HITD	head impulse testing device
HITD-FT	head impulse testing device – functional testing
HME	head movement emphasized
OINV	opioid-induced nausea and vomiting
PONV	post-operative nausea and vomiting
vHIT	video head impulse test
VOG	videooculography
VOR	vestibulo-ocular reflex

List of Publications

Peer-reviewed journals

Lehnen N, **Ramaioli C**, Todd NS et al. Clinical and video head impulses: a simple bedside test in children. *J Neurol 2017 May; 264(5):1002-1004. doi: 10.1007/s00415-017-8450-y.*

Ramaioli C, Colagiorgio P, Sağlam M, Heuser F, Schneider E, et al. The Effect of Vestibulo-Ocular Reflex Deficits and Covert Saccades on Dynamic Vision in Opioid-Induced Vestibular Dysfunction. *PLoS ONE 2014 Oct 20; 9(10): e110322. doi: 10.1371/journal.pone.0110322.*

Heuser F, Schulz C, Sağlam M, **Ramaioli C**, Heuberger M, Wagner KJ, et al. Preventing opioid-induced nausea and vomiting: Rest your head and close your eyes? *PLoS ONE 2017 Mar 14;12(3): e0173925. doi: 10.1371/journal.pone.0173925.*

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