NEUROPHYSIOLOGICAL CHANGES DURING ADAPTATION TO MOTION SICKNESS.

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ABSTRACT

"Torso Rotation" (TR) is an unusual motor strategy producing an acute, reversible change in vestibular function. Following a single exposure, the signs and symptoms of motion sickness appear along with gaze and postural instability and perceptual illusions during movement. Upon repeated exposure, motion sickness susceptibility disappears and gaze instability (measured during voluntary head shaking in the light) is reduced. Whole body step rotation in the dark demonstrated that the reduction in post-TR gaze instability occurred despite a consistent daily suppression of VOR gain. To evaluate the potential role of alternate sensory inputs in this long-term change, gaze stability was measured during head shaking in the dark (i.e. no visual inputs) and during *en bloc*, "head-and-torso" shaking in the dark (i.e. no visual and no cervical inputs). These experiments demonstrated that the day-to-day improvement in post-TR gaze stability was due solely to visual inputs. The cervico-ocular reflex and predictive mechanisms were not involved. Furthermore, the frequency-independent suppression of gaze stability caused by TR, its time course of recovery, and its parallel effects on postural control all suggest that this type of motor strategy involves a novel suppression mechanism, having widespread effects. Without implying causality, it is proposed that the similarity between the time course of adaptation to TR-induced motion sickness and the long-term reduction in gaze instability might reflect a common underlying mechanism. The latter would involve a de-emphasis of vestibular inputs and increased use of other sensory modalities, leading to a generalized, transferable type of adaptation. Subjective reports support this idea, as "adapted" participants mentioned decreased susceptibility in other, quite different provocative environments.

The dual nature of adaptation to motion sickness, being partly specific and partly transferable, is not a new concept. However, these experiments suggest that, through self-generated vestibular suppression, it might be possible to isolate and exploit the transferable aspect.

RÉSUMÉ

L'utilisation d'une stratégie motrice inhabituelle impliquant des rotations en bloc du torse et de la tête ("Torso Rotation", TR) crée des changements temporaires et réversibles de la fonction vestibulaire. Une fois terminé, cet exercice est suivi de symptômes du mal des transports, d'instabilité visuelle et posturale ainsi que de perceptions erronnées lors de mouvements normaux. Suite à plusieurs sessions impliquant TR, les symptômes du mal des transports disparaissent et l'instabilité visuelle diminue (telle que mesurée lors de mouvements rapides de la tête en présence d'une cible visuelle fixe) . Cette diminution de l'instabilité visuelle a lieu malgré une réduction répétée du réflexe vestibulo-oculaire (étudié à l'aide de rotations passives du sujet dans le noir). De façon à évaluer l'apport potentiel d'autres modalités sensorielles à ce changement graduel, le niveau de stabilité visuelle fût, par la suite, mesuré lors de mouvements rapides de la tête dans le noir (càd sans signaux visuels) ainsi que lors de mouvements combinés du torse et de la tête (càd sans signaux visuels ni cervicaux). Ces expériences ont démontré que seuls les signaux visuels sont impliqués, sans apport supplémentaire ni du réflexe cervico-oculaire, ni de mécanismes préventifs. De plus, d'autres changements causés par TR tels que: (1) l'atténuation globale (et donc non-dépendante de la fréquence étudiée) de la stabilité visuelle, (2) le processus de retour à la normale de la fonction vestibulaire, ainsi que (3) l' effet produit sur le contrôle postural, nous portent à croire que cette stratégie motrice utilise un nouveau mode d'atténuation, ayant des retombées plus globales. La similitude entre le processus d'adaptation au mal des transports et celui d'amélioration de la stabilité visuelle suggère que ces derniers reflètent possiblement l'utilisation commune

de certains mécanismes sous-jacents. Cette nouvelle forme d'atténuation impliquerait une diminution du rôle des signaux vestibulaires accompagnée d'une accentuation de celui d'autres modalités sensorielles, amenant donc une adaptation généralisée ainsi que transférable à d'autres milieux. Cette idée est compatible avec des commentaires rapportés par nos sujets, qui, une fois "adaptés", sont moins portés à être malades dans d'autres situations. Le fait que l'adaptation au mal des transports est en partie très spécifique à l'environnement en cause ainsi que partiellement transférable n'est pas nouvelle. Il est ici proposé que l'utilisation de mouvements causant une atténuation vestibulaire pourrait, cependant, permettre l'isolement et l'exploitation du côté transférable.

À mes parents

et à mes deux Nathalie,

de tout mon coeur.

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PREFACE

According to the Guidelines for Thesis Preparation published by the Faculty of Graduate Studies and Research of McGill University (September 1995 Revision), the thesis «dissertation can consist of (...) a collection of papers that have a cohesive, unitary character that allows them to be considered as a single programmatic research product». This option has been selected for the present thesis.

As requested, the following five paragraphs concerning the detailed Faculty regulations regarding thesis submission are included below:

> Candidates have the option of including, as part of the thesis, the text of one or more papers submitted or to be submitted for publication, or the clearly-duplicated text of one or more published papers. These texts must be bound as an integral part of the thesis.
>
> If this option is chosen, connecting texts that provide logical bridges between the different papers are mandatory. The thesis must be written in such a way that it is more than a mere collection of manuscripts; in other words, results of a series of papers must be integrated.
>
> The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation". The thesis must include: A Table of Contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a comprehensive review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.
>
> Additional material must be provided where appropriate (e.g. in appendices) and in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.
>
> In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsabilities of all the authors of the co-authored papers.

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General Introduction.

RATIONALE

Hippocrates wrote (Sec. iv; Aph. xiv) that "sailing on the sea proves that motion disorders the body". Regrettably, thousands of years later, our understanding of motion sickness has not advanced very much beyond this point.

Output pathways (autonomic circuits, brainstem nuclei, etc.) have been described, but little has been learned concerning how these responses are generated. Even less is known about how *adaptation* to motion sickness occurs. Until more is known about these underlying mechanisms, rational means of prevention or treatment will remain elusive.

In the work presented here, a unique model of self-generated motion sickness was used to examine changes in vestibular function during adaptation to that stimulus.

The results support the existence of a generalized, transferable type of adaptation, and provide evidence as to how this is achieved.

ORGANIZATION OF THE THESIS

The primary goal of the thesis is presented above. Chapter 2 provides a broad overview of general concepts taken from the literature. More specific references will be found in the Introduction and Discussion sections of the following Chapters. Chapter 3 summarizes current knowledge of the "Torso Rotation" method and its acute effects. Chapters 4-8 consist of detailed presentations of the experiments performed as part of this thesis project. They are in the form of original papers, either submitted to the Journal of Vestibular Research (4-6) or in preparation (7-8). Chapter 9 is a brief summary of the contributions of this thesis to original knowledge.

Literature Review.

MOTION SICKNESS

ACUTE ASPECTS

Signs and Symptoms

Motion sickness is a sometimes debilitating syndrome that was already recognized by the Ancient Greeks thousands of years ago (1). It is defined by a series of signs and symptoms that can be divided into 3 categories: autonomic, psychological, and other. Different combinations of these symptoms can be experienced depending on the individual and on the provocative situation. Autonomic signs and symptoms include pallor, cold sweating, stomach awareness, stomach discomfort, flushing, flatulence, belching and salivation. Psychological factors include drowsiness, apathy, mental confusion and general malaise. Finally, the third category includes headache, nausea, retching and vomiting. It should be pointed out that severe motion sickness can be experienced without the appearance of vomiting, however (1, 2).

Provocative Situations

Motion sickness has been reported in a wide variety of situations that can be divided according to the following: unusual environment, damaged transducer, or inappropriate central processing. (a) Unusual environment. In every day life, we are exposed to relatively narrow frequency bands of linear and angular movement as well as to the constant 9.8 m/s^2 (1 "g") gravitational acceleration of the earth. Furthermore, our visual surrounding does not usually move spontaneously. If the acceleration or visual environment is changed so as to generate inputs outside the normal operating range of the body, motion sickness can result. Provocative situations falling into this category include: the different modes of transportation (car, airplane, ship, reviewed in 1), acrobatic (3) parabolic (4) and space flight (5-7),

flight simulators (8, 9), slow rotation rooms (10, 11), scuba diving (12), centrifuges (13) and passive visual stimulation (14, 15). The effectiveness of the latter stimulus indicates that actual *physical* motion is not always necessary to provoke motion sickness. (b) Damaged Transducer. Inappropriate sensory information can be transmitted to the central nervous system (CNS) and cause motion sickness if the vestibular labyrinth is damaged. This could result from trauma, infection, degenerative processes such as Meniere's disease, ototoxicity following treatment with antibiotics such as Gentamicin (16), or surgery (labyrinthectomy, VIIIth nerve transection or damage during removal of an acoustic neuroma). In all cases, only one labyrinth has to be affected for motion sickness symptoms to appear (17). (c) Inappropriate Central Processing. Finally, the environment and the vestibular labyrinth might both be normal, but the processing of incoming sensory information might have been altered by wearing vision modifying spectacles (18, 19), by performing "Torso Rotation" (see Chapter 3) or by acute brainstem pathology. In any of these cases, motion sickness is likely to appear.

Lack of Correlation

There is no clear correlation between the different types of motion sickness. For example, an individual suffering from seasickness will not necessarily be affected by airsickness. This finding creates problems when trying to select candidates to work in provocative situations requiring high levels of performance (e.g. space flight, 20). Extremely sensitive individuals will get sick in essentially any situation, however.

Reason's Sensory Conflict Theory

Thus, motion sickness is a complex malady that can appear in a wide variety of situations. In an effort to bring together all of the seemingly incoherent information in this field, Reason proposed a unifying model, the 'sensory conflict theory' (21). According to this model, there is only one kind of motion sickness. During a given movement, the CNS is expecting a given combination of sensory inputs, based on recent past experience. If for some reason (environmental, pathological, etc.) the sensory signals relayed to the CNS do not match the ones that are expected, a sensory conflict occurs and motion sickness appears.

ADAPTATION TO PROVOCATIVE SITUATIONS

Time Course

As debilitating as motion sickness can be, it is normally a transient phenomenon. If a susceptible individual remains in a provocative situation for a prolonged period of time, signs and symptoms will gradually decline, with complete disappearance after 2 to 3 days. This process is variously referred to as *adaptation, habituation or desensitization*. Its time course is remarkably constant from one situation to another (6, 22, 23). The mechanisms involved in the adaptation process don't require continuous stimulation: short, repeated sessions can be just as effective (e.g. 2).

Mal de Débarquement

The 'adaptive immunity' that one develops after prolonged exposure to a provocative stimulus is not retained forever. It gradually disappears over a few weeks if one is not re-exposed to the stimulus. Motion sickness can also be experienced immediately upon *leaving* the provocative situation. This

particular situation has been called *mal de débarquement* (1, 21, 24, 25) and is well known to sailors and astronauts.

Reason's Update of 'Sensory expectations'

According to Reason's model, adaptation is the result of the CNS updating internal 'maps' of expected sensory combinations (21). Once adaptation is complete, there would be less conflict between expected and actual inputs. After a long voyage at sea , returning to land would cause a *new* conflict and motion sickness could be experienced once again as mal de débarquement.

There are limitations to Reason's model. One is the problem of how adaptation occurs in situations where motion is unpredictable (26). Another is that it does not define the underlying neural circuitry (27). Nevertheless, it represents a major step forward in our understanding of *when* motion sickness can arise.

There may also be other forms of adaptation. Dobie and May (28) have written «there are both specific and general components in learning to tolerate motion environments». Reason's model would result in specific, non-transferable protection. In contrast, adaptation to "Torso Rotation" (Chapter 3) seems to result in a kind of general adaptation that *is* transferable to other motion environments (see Chapters 4 and 5).

CIRCUITRY

Historically, the autonomic nervous system, two brainstem centers and the cerebellum have been thought to play a role in the direct production of motion sickness signs and symptoms. A role for higher centers has also been described (1). Unfortunately, the anatomy of the more central neural

pathways responsible for initiating motion sickness in the first place are essentially unknown (29).

Autonomic Nervous System

Motion sickness signs and symptoms such as facial pallor and cold sweating demonstrate the involvement of the autonomic nervous system. This is probably mediated through vestibular system - reticular formation connections (30, see below).

Brainstem Centers

Two areas have been identified in the brainstem that seem to be necessary for the development of motion sickness. These are the 'chemoreceptive trigger zone' (CTZ) and the 'vomiting center' (VC). Normally, stimulation of the former would lead to activity in the latter, followed by emesis. The functional connections between the labyrinths, the CTZ and the VC are not that clear, however, and may include chemical rather than neural links in some cases. The VC is quite controvertial and its existence has even been questioned (22, 23, 31-34).

Cerebellum

Removal of the entire cerebellum, and in particular the nodulus and uvula, leads to greatly increased resistance to motion sickness (1). This area of the brain might also be expected to participate in adaptation to the disorder, but this has yet to be demonstrated.

Higher Centers

The presence of psychological symptoms as an integral part of motion sickness suggests the involvement of the cerebral cortex (1). Based on studies showing that denervation of the gut does not prevent vomiting and that the

somatic musculature is very much involved in this highly coordinated process, Money (35) has pointed out that even vomiting involves higher centers.

THE VESTIBULAR SYSTEM

NECESSARY FOR MOTION SICKNESS

In a series of comparative studies, individuals without vestibular function (labyrinthine-defective, LD) and normals were exposed to a number of very provocative situations including acrobatic flight (3), parabolic flight (4), rough seas (36), a slow rotation room (10, 11), and passive visual stimulation (15). Unequivocal results were obtained in all cases: unlike normals, LDs never got motion sick. These experiments demonstrated definitively that only individuals with a functioning vestibular system can be made motion sick.

GENERAL DESCRIPTION

Unique amongst the special senses, the vestibular system carries out most of its normal functions without our conscious perception (37). Some output does reach the cortex, however, providing a sense of spatial perception and self-motion (37-41). Compared to normal function, vestibular pathology is very noticeable and often quite debilitating. A classical description of the symptoms was published by Crawford (42), following his personal experience of bilateral loss of function.

Unless otherwise indicated, the general description of the vestibular system (labyrinth and associated nuclei) given below was derived from the extensive reviews of Goldberg and Fernández (43) and Wilson and Melvill Jones (44).

VESTIBULAR LABYRINTH

Anatomically and functionally, the inner ear can be separated into two regions: the cochlea, sensitive to sound, and the vestibular labyrinth, sensitive to movement and gravity. The membranous labyrinth consists of a closed system of interconnected fluid-filled ducts surrounded by a thin layer of epithelial cells. It is contained inside a bone cavity of similar shape, the bony labyrinth. The space between the bony and membranous labyrinth is filled with perilymph (similar to cerebrospinal fluid) and the membranous labyrinth is filled with endolymph (similar to intracellular fluid). Inside each membranous labyrinth, two types of specialized sensors are found: three semicircular canals (SSC) and two otolith organs. The SSCs are stimulated by angular accelerations, and the otoliths by gravitational and inertial linear accelerations (45). As an ensemble, the semicircular canals and otoliths provide the CNS with a complete, 6 degrees of freedom inertial guidance system.

Canal Transduction

The SSCs can be simplified as 3 independent fluid-filled rings. At one point along each ring, an elastic membrane (the cupula) completely blocks the passage of fluid. When the head turns, the SSC turns with it. The liquid inside the SSC is left behind, and exerts a pressure on the elastic membrane, which deforms slightly. Receptor cells (hair cells) located at the base of the cupula (crista) transduce the mechanical deformation into nerve impulses that get transmitted to the brain by the vestibular branch of the VIIIth cranial nerve. Semicircular canal dynamics are such that angular *velocity* and not acceleration, is transduced over the frequency range of normal head movements (0.1 - 5.0 Hz, 44). Being essentially orthogonal to each other, the 3 SSCs can sense angular velocity about any axis.

Otolith Transduction

The two otoliths are also functionally independent. Each one consists of an oblong mass of calcium carbonate crystals (the otolith) secured on one side to a group of hair cells. When the head is translated along the plane of the otolith, this relatively denser mass is left behind, bending and hence activating the hair cells. The dynamics of this system are quite different from those of the SSCs. First, linear acceleration and not velocity is transmitted to the CNS. Secondly, the frequency response ranges from DC to at least 2 Hz. The DC component therefore makes the otolith organs also sensitive to gravitational acceleration. Thirdly, unlike inside the SSC cristae, hair cell orientation in the maculae is not uniform, with the result that linear acceleration in all 3 planes is transduced by only 2 otolith organs.

Output Pathways

Nerve afferents from the vestibular system enter the CNS via the vestibular branch of the VIIIth cranial nerve. Most terminate on the different vestibular nuclei, while some go directly to the cerebellum and terminate in the flocculus and nodulus (30).

Projections to the Labyrinth

There is anatomical evidence that the vestibular system receives efferent innervation, but the physiological role of such pathways remains unclear (46-49). Other projections have also been reported (sympathetic innervation, receptor-receptor neurons) which also require functional clarification (43).

VESTIBULAR NUCLEI AND BEYOND

Primary afferents from the different parts of the ipsilateral labyrinth make excitatory connections within the vestibular nuclei (reviewed in 41). The latter also receive inhibitory inputs from the contralateral side, through the commissural pathway. Canals lying in similar planes on the two sides of the head therefore operate in push-pull pairs. It is not so clear if the otolith organs operate in a similar fashion. From the vestibular nuclei, secondary vestibular neurons send axons to a variety of sites, including the vestibular cortex (50), the cerebellum (1, 44), the spinal cord (43, 44, 51), the oculomotor nuclei (52, 53), the reticular formation (30, 51), and the autonomic nervous system (1). Some of these pathways are involved in generating reflexes stabilizing the eyes (vestibulo-ocular, see later in this Chapter), the head (vestibulo-collic, 54, 55) or the body (vestibulo-spinal, 44) relative to space.

VESTIBULAR COMPENSATION

Damage to a vestibular end organ leads to severe incapacitation. Symptoms include gaze and postural instability, vertigo, and sometimes motion sickness. These symptoms disappear in a matter of days or weeks, however, in a process called *vestibular compensation*. The classical explanation of this process is the take over of the ipsilateral vestibular nuclei (VN) by the contralateral labyrinth through plastic adaptation of the CNS. There is now mounting evidence that relatively little recovery occurs centrally *per se*. Instead, substitution of other sensory inputs might be the main source of the apparent behavioral improvement (17).

ASSOCIATION BETWEEN MOTION SICKNESS, THE VESTIBULAR SYSTEM, AND EYE MOVEMENTS

Over the last 25 years, motion sickness has been reported repeatedly in association with changes in the normal function of the vestibulo-ocular reflex (VOR, described below). Examples include wearing vision-reversing goggles (18, 19), parabolic flight (26), and space flight (56). It should be noted that such a correlation could not be *causal*, as blind people, who do not require a functional VOR, can still be made motion sick (57). Nevertheless, it led to the proposition that perhaps the process of adaptation to motion sickness could be *reflected* in the VOR circuitry (26, 56).

THE CONTROL OF EYE MOVEMENTS

Compared to other motor systems, the control of eye movements is relatively simple. First and foremost, the CNS only has to take into account 3 degrees of freedom (rotations, not translations). Furthermore, the mass of the eyeball is small and can be ignored in movement planning (58).

According to Robinson (59), eye movements can be divided into 5 categories: saccadic, optokinetic, pursuit, vestibulo-ocular, and vergence. The latter is not involved in the work presented in this thesis and will therefore be left out of the discussion, being replaced by a more relevant section on the cervico-ocular reflex.

COMMON ANATOMY

Each eye is controlled by a total of 6 muscles (60). Motoneurons innervating these muscles originate from 3 different cranial nerve nuclei (61): the oculomotor nucleus, controlling the inferior oblique, medial, inferior and superior rectus muscles; the trochlear nucleus, controlling superior oblique; and the abducens nucleus, controlling lateral rectus.

VESTIBULO-OCULAR REFLEX (VOR)

Linear VOR

This discussion will concentrate on the *rotational* VOR. It should be noted, however, that eye movements have also been described following translational movements of the head, generated by the so-called linear VOR (62). The study of this system is more recent, and much remains to be learned about its anatomy, physiology and normal role.

Rotational VOR

(For clarity, all further references to the term VOR will imply the rotational VOR). The role of the VOR is to stabilize the eyes in space during head perturbations (voluntary or involuntary) and therefore maintain visual acuity (44). The most direct pathway consists of a simple 3 neuron arc from the vestibular labyrinth to the eye muscles (52). The activation dynamics of the eye muscles are such that the basic velocity signal provided by the direct pathway has to be supplemented by an eye position signal, speculated to be computed by a central 'velocity-to-position' neural integrator, the exact anatomical location of which is not entirely clear (see 63). In addition, theoretical calculations based on SSC dynamics predict that prolonged whole body rotation in the dark should lead to an exponential decay of eye velocity with a time constant under 10 seconds in humans (44). Experimental measurements yield larger values, up to 20 seconds. This improvement in the frequency response of the VOR compared to its SSC input is thought to result from a neural 'velocity storage' mechanism (64).

The VOR is very fast: compensatory eye movements are seen as early as 12 msec after the onset of head rotation in monkey (65). Such rapidity has a drawback: it does not allow enough time for processing feedback coming

from the eyes (66). On a moment-to-moment time scale, the VOR is therefore operating open-loop. Nevertheless, the VOR remains calibrated through life, despite aging and in some cases wearing prescription glasses, situations that call for different gain values (66). Experiments performed in the early 1970s demonstrated that VOR calibration is maintained through visual feedback mechanisms (e.g. 18, 67). Implications of this mode of calibration will be discussed in another section (see VOR plastic adaptation, below). To be perfectly compensatory, the VOR should have a gain of -1, i.e. eye and head movements should be of equal size and opposite direction. In humans, VOR gain can be modulated substantially by volition (68). Furthermore, during passively applied whole body step rotations in the dark, small *compensatory* saccades can supplement the slow phase VOR (69, 70). Such findings have led some to question the term vestibulo-ocular *reflex* (71, 72).

OPTOKINETIC SYSTEM

At very low frequencies (including DC), image stabilization is provided by the optokinetic system. The latter is thought to have evolved to complement the VOR (59). It uses retinal image slip as a stimulus to generate eye movements. Head movements are not necessary. Most of the central circuitry used by the VOR is also used by the optokinetic system, including velocity storage (64).

In afoveate animals, such as the rabbit, constant movement of the visual field in a given direction will generate smooth eye movements in the same direction (slow phases) interspersed with rapid resetting movements in the opposite direction (quick phases). This type of response is called optokinetic nystagmus (OKN). During visual stimulation, slow phase velocity increases assymptotically, following a time constant similar to that of the VOR. In monkey, OKN is more complex (64). Initially, eye velocity rises in a

step fashion (direct pathway) and then continues exponentially to saturation (indirect pathway). The latter is though to represent the output of the velocity storage shared with the VOR. In humans, the direct pathway predominates (73).

SMOOTH PURSUIT

The primate retina can be divided into 2 functional areas: a central zone of high visual acuity, the fovea (color sensitive, small visual field) and a peripheral zone of lower visual acuity, color insensitive and covering the rest of the visual field (74). Many more details can be extracted from a point of interest if it resides on the fovea than if it remains in the periphery. Two types of eye movements have evolved to take advantage of this anatomical feature: the saccadic system (discussed below) quickly brings a point of interest to the fovea, and the pursuit system maintains the target on the fovea as it moves across the visual field.

The pathways involved in generating smooth pursuit have been reviewed by Tusa and Zee (75). Briefly, the visuo-cortical pathway involves the lateral geniculate body, the primary visual cortex (area V1), the extrastriate cortex (area V2) and visual association cortex areas MT (middle temporal) and MST (medial superior temporal). There are two corticofugal pathways: i) from MST to the dorsolateral pontine nuclei (DLPN) and ii) from MT, posterior parietal cortex, MST and frontal eye field, to the nucleus reticularis tegmenti pontis (NRTP). The 2 pathways then join at the level of the cerebellum and go down to the vestibular nuclei, the abducens, and finally the extraocular muscles. The gain of this system is essentially flat from DC to 0.4 Hz (40-60°/sec peak target velocity), and then falls off rapidly between 0.5-3.0 Hz (76).

Following classical arguments, pursuit is driven by the velocity of target slip across the retina and the predictability of the stimulus (77, 78). The relative importance of these factors is not entirely clear as yet, as recent experiments by Barnes and co-workers have shown that smooth pursuit can be generated in humans in the complete absence of a moving target (79, 80).

The pursuit and optokinetic systems are not independently driven by the morphologically different central and peripheral retina, respectively. There have been multiple reports showing that, at least in humans, there is no clear anatomical separation between these systems. Pursuit can be triggered by a target moving in the periphery (81) and optokinetic nystagmus by a central stimulus (82-85). Nevertheless, the 2 systems co-exist and provide complementary control of the eyes, perhaps in a more complex way than expected at first glance.

SACCADIC SYSTEM

The role of the saccadic system is to bring objects of interest on the fovea, the central zone of the retina having the highest visual acuity. Saccades are characterized by extremely rapid eye movements (peak velocity up to 600°/s in humans). The gross anatomy of the pathways controlling saccades include the frontal eye field, the superior colliculus, the cerebellum and the oculomotor nuclei. Saccade size can vary tremendously, from about 3 min. of arc to 90° (reviewed in 59). Peak eye velocity during a saccade is related to the amplitude of the resulting movement: the higher the peak velocity, the larger the movement will be. When scanning a room, saccades appear at a rate of about 3 per second (59). Under certain laboratory conditions, successive saccades can be generated with a delay of only 100 msec, however (86). The classical scheme of activation for saccade generation implied that the superior colliculus was the last step at which signal

modifications could occur. A review of recent evidence questions this interpretation (87).

CERVICO-OCULAR REFLEX (COR)

Following bilateral labyrinthectomy, the gaze stabilizing action of the VOR disappears. Classical experiments by Dichgans et al. (88) showed that part of the gaze stability recovery after labyrinthectomy in the monkey came from the emergence of a reflex that used neck muscle stretch as a stimulus to generate compensatory eye movements, the so-called cervico-ocular reflex (COR). Some time after surgery, if the head of the body-fixed animal was rotated passively in the dark, slow phase eye movements were generated in a direction opposite to the head movement. The existence of the COR was later confirmed in labyrinthine-defective human beings (89-92). Underlying neural circuitry has remained undefined, partly due to the complexity of the neck muscle plant (see 93). However, there is a wide body of evidence suggesting that the COR does not participate to gaze stabilization in normals (89, 90, 94-97). The frequency response of the "enhanced" COR is also quite low, becoming essentially nil above 0.4 Hz (e.g. 89). Since smooth pursuit can function up to more than 1.0 Hz, the COR seems somewhat unsutable as a replacement for a deficient VOR.

VISUAL-VESTIBULAR INTERACTIONS

NORMALS

In normal life, image stability on the retina results from the combined action of the VOR and visual mechanisms (98-101). Visual and vestibular information merge at the level of the vestibular nuclei (102). Beyond that stage, the brain can no longer differentiate between the two unless other cues are available. One of the consequences of this shared anatomy is a series of

illusions, the most commonly experienced probably being vection (reviewed in 38). Vection is a subjective impression of self-motion driven by a purely visual stimulus. A common example of linear vection reported by car drivers is the feeling of their vehicle starting to move backwards when they are stopped at a red light. In fact, they are not moving at all, but the vehicle beside them is moving forward slowly, thereby stimulating their peripheral retina. Circular (angular) vection is often experienced in wide-screen movie theatres when the scene suddenly tilts.

VESTIBULAR MODIFICATIONS

The relative contributions of vision and vestibular inputs can be assessed in normals and people with altered vestibular function (e.g. labyrinthine-defective patients or astronauts) using tests involving conflicting visual and vestibular inputs. Two common tests are the Equitest (103) and circular vection (104), looking at the relative importance of visual versus vestibular inputs on postural control and self-motion perception, respectively. Overall, subjects with vestibular problems tend to become more visually dependent than normals (103, 105, 106).

VOR PLASTIC ADAPTATION

As mentioned before, the VOR does not use direct feedback from extra-ocular muscles. Yet, as one grows up and ages, or starts wearing prescription glasses, the VOR remains adequately adjusted to these sometimes quite different demands (66). What is (are) the signal(s) used to calibrate the VOR?

CHANGING THE VISUAL GOAL

The first demonstration that visual inputs played a key role in VOR calibration was provided by the behavioral experiment of Gonshor and Melvill Jones (18, 67). The rationale for this experiment was:

«If active homeostatic mechanisms are at play in retaining the normal state of affairs, then presumably abnormal conditions should force adaptive rearrangement of central controlling parameters to produce a matching alteration of sensory-motor relations in the reflex.» (107).

The 'abnormal condition' consisted of forcing subjects to perform normal activity while wearing left-right vision reversing dove prisms. When the head moved left, the visual scene now moved *with the head* instead of away from it. As a result, the normal response of the VOR *destabilized* the image of the outside world on the retina. If the goal of the VOR is to help in image stabilization during head movement, then prolonged exposure to vision reversal should eventually reverse the reflex. Indeed, experimental results confirmed this prediction and led to a number of other studies demonstrating the adaptability of the VOR to essentially any new visual goal dictated by different types of optical devices, both minifying (e.g. 108, 109) and magnifying (e.g. 108-113). Following 'recalibration', if the person or animal was maintained in the dark, the *adapted* state remained until a new visual goal was presented, demonstrating the *plastic, goal directed* nature of the change (18).

MODELS AND ANATOMY

A thorough description of the different mathematical models of VOR adaptation is beyond the scope of this section. Instead, emphasis will be put on the anatomical implications of two structural models, pertinent to some facets of the work presented in the following Chapters. Detailed reviews concerning these models are available in the literature (65, 114-116).

The Flocculus Hypothesis

Using the rabbit (an afoveate animal) as a model, Ito, based on the Marr-Albus theory of cerebellar function (117, 118), proposed that the site of plastic VOR gain modifications could be located inside the cerebellum. More

specifically, the change could occur at the parallel fiber-Purkinje cell junction, through heterosynaptic interactions involving climbing fibers. Assuming an inappropriate VOR gain, Ito's model can be summarized as follows: as a head movement is generated, impulses from the labyrinth are sent both to the vestibular nuclei (via primary afferents) and to the cerebellum (via a mossy fiber-granule cell pathway). In the meantime, through the direct VOR arc, a compensatory eye movement is generated, the size of which does not match the head movement, resulting in image slip. The image slip signal is relayed to the cerebellum as an 'error in performance', via climbing fibers. According to the Marr-Albus theory, the climbing fiber signal acts as a 'teaching line', modifying the efficacy of the parallel fiber-Purkinje cell synapse. Purkinje cells, the main output pathway from the cerebellum, are known to have a powerful inhibitory effect on relay cells of the VOR (43). It is therefore conceivable that changes in the mossy fiber-Purkinje cell loop gain would modify the gain of the VOR. Electrophysiological and ablation studies demonstrated that i) climbing fibers carried appropriate visual information (119, 120) and ii) removal of the cerebellum prevented VOR adaptation (see 114 for references).

The Brainstem Hypothesis

Studies by Miles and co-workers in the monkey (a higher vertebrate having a fovea) suggested an alternative hypothesis (reviewed in 65). Essentially, plastic changes would occur *in the brainstem,* with the participation of the cerebellum. There were two main reasons for this hypothesis: i) cerebellar Purkinje cells in the monkey have been shown to encode gaze velocity (movement of eye re space) and not only head velocity and ii) VOR adaptation causes concurrent changes in OKN (121), a system sharing pathways with the VOR (see optokinetic system, above).

Regardless of which model or combination of models best represents the adaptation process, the two presented above emphasize the importance of a number of anatomical structures including the brainstem, the cerebellum and the inferior olive. In humans, the fact that VOR gain can be decreased without visual inputs *under certain conditions* (122, see below) suggests that some cortical pathways might also take part in the process.

VOR SUPPRESSION

Under certain conditions, a gaze stabilizing reflex such as the VOR can be counterproductive (e.g. looking at one's hand while running, or reading instruments in a manoeuvering aircraft). In both situations, the VOR tries to maintain the eyes fixed relative to space while the individual wants to keep them on objects moving with him. If the perturbations have a low enough frequency content, it is possible to *suppress* the VOR. As the frequency content increases, the VOR gradually takes over and the hand or instrument panel becomes blurred. In the laboratory, VOR suppression has been studied during self-generated and passively applied movements.

DIFFERENT TYPES OF MOVEMENTS, ONE TYPE OF RESPONSE

Active VOR suppression can be studied during combined eye-head tracking (e.g. 123, 124) or voluntary head-shaking while following a real or imagined head-fixed target (e.g. 125, 126). VOR suppression can also be generated by *passive* rotation of the body together with a real or imagined surrounding visual scene (e.g. 68).

The frequency response of this system is very similar to that of smooth pursuit. At first glance, one might therefore suggest that VOR suppression is the result of the summation of the VOR and a real or 'imagined' smooth pursuit signal. The situation appears to be more complex, however, since

dissociation between smooth pursuit and VOR suppression have sometimes been reported during neurophysiological and clinical experiments (summarized in 76 and 127). To account for these findings, Robinson (127) proposed that VOR suppression had access to the pursuit circuitry, an efferent copy (128) of planned head movements and a predictor of target motion. Depending on experimental conditions, this 'central suppressive mechanism' could be complemented by actual visual feedback (see 76).

SUPPRESSION-INDUCED CHANGES IN VESTIBULAR FUNCTION

Following a prolonged period of passive VOR suppression with a head-fixed visual surround, the gain of the VOR is decreased (69). This would be expected if one considered VOR suppression to simply be an extreme case of VOR adaptation, having as a goal a VOR gain of zero. Similar results have been obtained after prolonged *active* suppression in the dark, *but not after passive movements* (122). The latter results leave open the question of the nature of the long-term effects of VOR suppression.

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A Review of the Acute Effects of "Torso Rotation"

HISTORICAL ORIGIN OF "TORSO ROTATION"

These experiments evolved from several independent observations. Guitton noted that substituting for a neck brace by *voluntary*, en bloc movement of the head and torso can gradually lead to motion sickness. Watt observed that a similar motor strategy is often adopted in weightlessness, an extremely provocative environment, and proposed the term "Torso Rotation" (TR) to describe it. While TR can be an effective means of reducing head movements to control symptoms (1), it is often used before any illness develops. Therefore, it was suggested that the method used to reduce space motion sickness in the short term might actually be counter-productive over a longer time scale. This led to the present studies of TR and adaptation to self-generated motion sickness.

"STANDARD TORSO ROTATION"

For laboratory use, an exaggerated and controlled version of TR was designed. Instead of walking around in a somewhat random fashion, subjects were instructed to stand in one place and to sweep their eyes back and forth between two targets located 135° on either side of straight ahead. To see the targets without moving the feet, combined movements of the eyes (±135°), head (±90°) and torso (±45°) were necessary (Figure 3.1). To accomplish this, and in contrast to more usual kinds of movements, subjects had to strongly and nearly continuously suppress vestibulo-collic and vestibulo-ocular reflexes. The pace and duration of the conditioning were set at 0.7 Hz and 30 minutes respectively, on empirical grounds. As expected, this technique was more effective at causing symptoms of vestibular dysfunction and motion sickness than the original form of TR. Most of our work has been done using this newer method, referred to as "standard Torso Rotation".

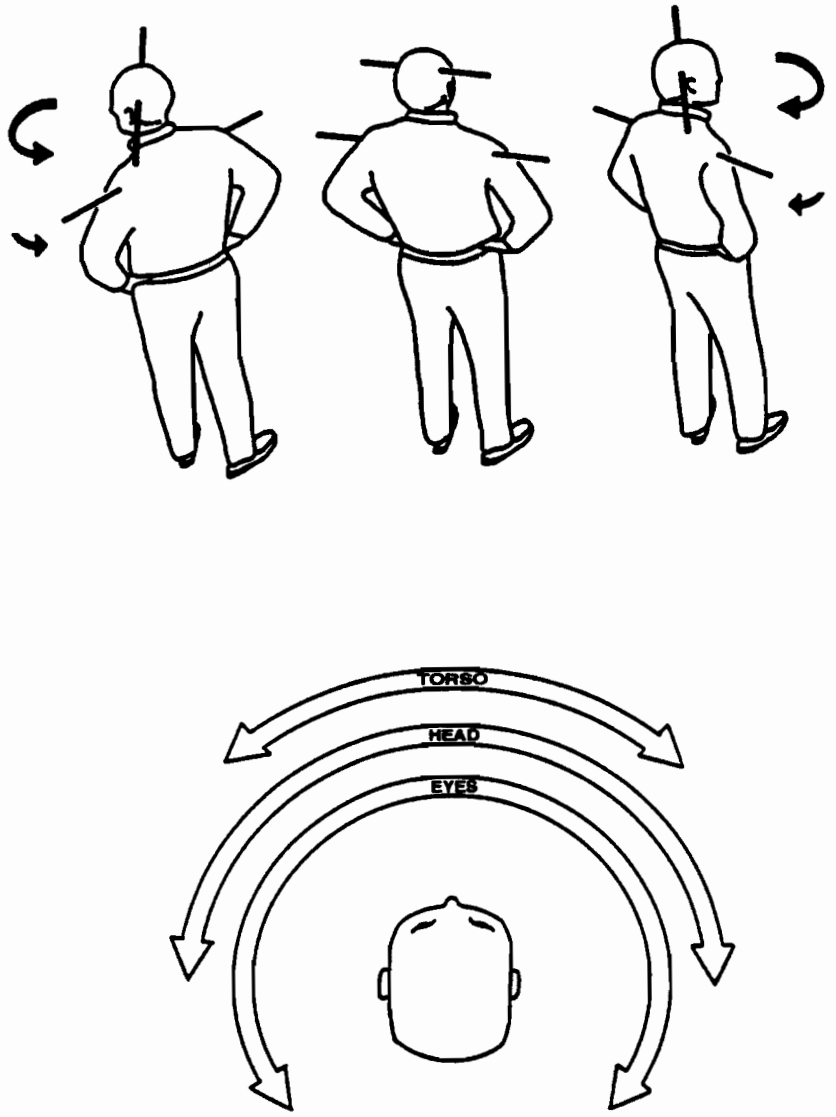

Figure 3.1 Standard "Torso Rotation" consists of reorienting gaze (eye re space) between two targets located 135° to either side of straight ahead. Combined movements of the eyes, head and torso are necessary to perform this task. The visual axis sweeps the largest angle (270°), the head moves less (180°), and the torso moves least (90°).

Figure 3.2 shows that TR consists of a continuous series of very large gaze refixations, where the subject shifts his visual axis to one target, tracks it as the head reverses direction, then shifts his visual axis to the alternate target, and so on. Peak head displacement and velocity in this example are ± 115° and ± 500°/s, respectively. The torso moved ±60° at a peak velocity of ± 280°/s. Peak eye displacement could not be measured accurately due to non-linearities in the EOG signal for large eye angles (>30°). It is approximately ± 45-50°, i.e. close to the 'neural' oculomotor range limit (2). The frequency was also quite stable, oscillating between 0.69 and 0.71 Hz. In summary, standard TR is a repetitive, self-generated and deceptively simple movement (akin to very large gaze refixations) that can be performed easily, consistently and for prolonged periods.

THE EFFECTS OF STANDARD TR

After 30 minutes of standard TR, subjects experience gaze and postural instability, perceptual illusions during movement and sometimes a remote, trance-like feeling. If forced to move around substantially, varying levels of motion sickness appear (3). Among the signs and symptoms are pallor, cold sweating, stomach discomfort, general malaise, salivation, belching, yawning, flushing, mental confusion, apathy, drowsiness, retching, and vomiting. Any combination of these symptoms is possible, experienced to varying degrees by different individuals. Vomiting is extremely rare, primarily because subjects are encouraged to slow down or stop moving before reaching that stage. Most of the subjective effects gradually disappear within the 20 minutes following TR, although a mild level of general malaise often persists for hours.

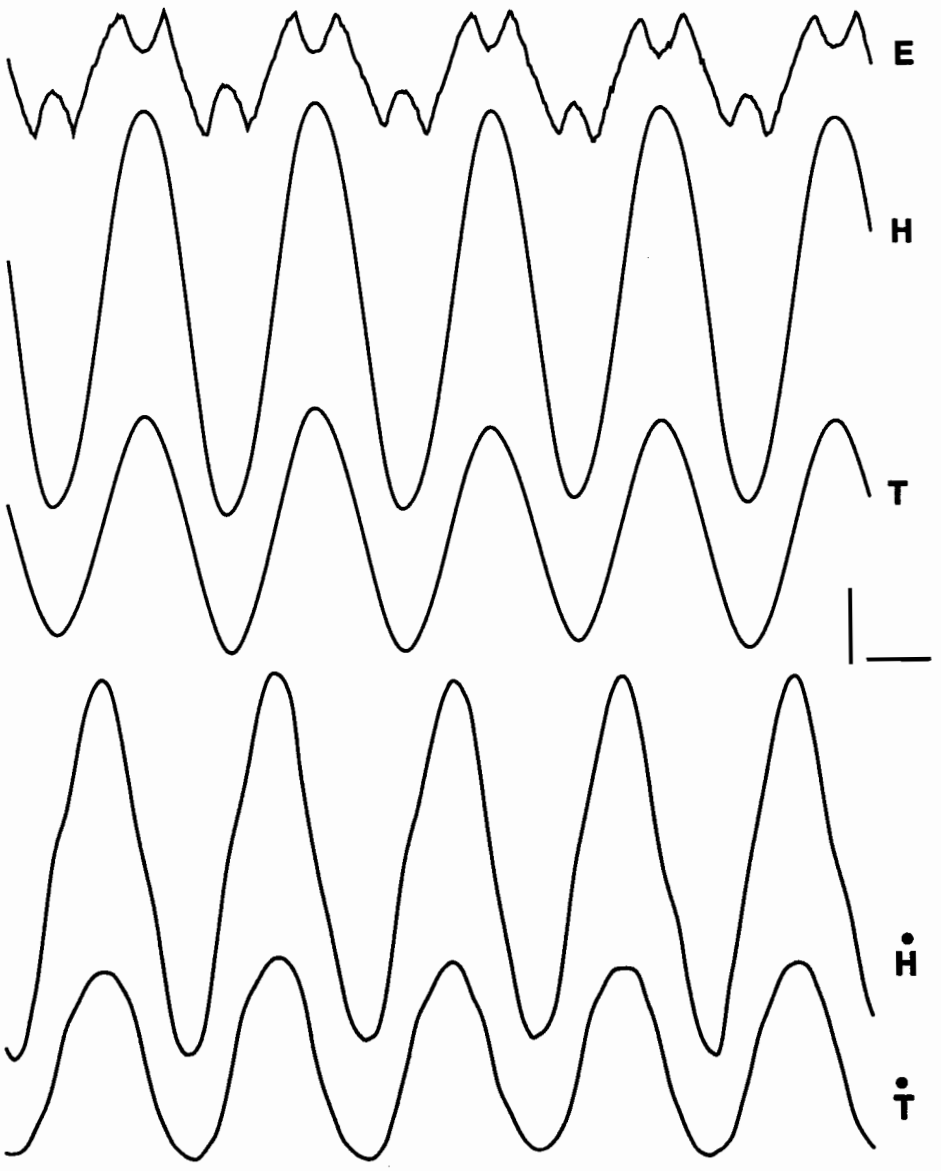

Figure 3.2 Performing TR is a very stereotyped task, as shown by the above recordings taken during an actual 30 minutes conditioning session. **E**, **H** and **T** represent eye , head and torso position, respectively. Standard electrooculography was used to measure eye movements and rate sensors were used to measure head and torso angular velocity. Head and torso positions were calculated by integration of head and torso velocity, also shown on this figure ($\dot{H}$, $\dot{T}$). The vertical scale represents 40° or 200°/s and the horizontal scale represents 0.5 s.

TR also causes numerous changes that can be measured objectively. In total, Tables 3.1 and 3.2 summarize eighteen experiments carried out so far. The measures can be divided into two groups: formal experiments, carried out on a statistically meaningful number of subjects (Table 3.1), and preliminary results, testing new ideas and/or providing background data for more formal measurements (Table 3.2). It should be emphasized that the areas presented in these tables have not all been investigated to the same extent. Yaw axis gaze control has received most attention so far, partly for historical reasons but also because technically, small changes can be detected reliably.

The positive findings in the tables demonstrate that TR causes broad changes in vestibulo-ocular function (tests 1.1, 1.2, 1.8, 1.9, 2.1), vestibulo-spinal function (tests 1.4, 1.10, 2.3, 2.4, 2.5, 2.8), visual-vestibular interactions (test 2.2) and vestibular perception (tests 1.3, 1.6). The negative findings, on the other hand, suggest that TR does not affect locomotion (test 2.6) nor does it alter ocular smooth pursuit, gaze holding or saccade generation (test 2.7). Linear VOR (test 1.7) and ocular counter-rolling, (test 1.5), respectively testing dynamic and static otolith function, suggest that standard TR does not affect the otoliths either. It is possible, however, that these methods are not sensitive enough to pick-up a 10-15% change. Further investigations will have to be carried out before conclusions can be drawn regarding the effects of TR on otolith function. Provided subjects move around actively, all the affected systems return to normal within about 20 minutes.

Table 3.1 - Formal experiments ($n \geq 6$).

Test		Method	Effects of "Torso Rotation"
1.1	Net vestibulo-ocular reflex (VOR) gain*	passive whole body step rotation in the dark while keeping eyes on imagined earth-fixed target (5).	significant reduction in gain (about 12%).
1.2	Smooth phase VOR	same as net VOR above. different group of subjects	about 15% reduction in smooth phase gain, i.e. net gain - saccades (6, 7).
1.3	Vestibular memory-contingent saccades (VMCS)*	rotation of body and eyes in the dark followed by eye saccade back to imagined target position (8).	significant reduction in gain, parallel to net VOR.
1.4	Vestibulo-collic reflex (VCR)*	passive trunk step rotation in the dark while keeping head on imagined earth-fixed target (9).	significant increase in gain.
1.5	Ocular counter-rolling (OCR)*	static, roll eye position following whole body tilt to the side (10).	no effects (P>0.25).
1.6	Luminous line test (LLT)*	orient luminous line with perceived vertical plane following passive whole body tilt to the side (11).	significant increase in deviation from actual vertical plane.
1.7	Linear VOR	interaural, whole body step translation in the dark while keeping eyes on imagined earth-fixed target (12).	no effects (P>0.45).
1.8	Gaze stability in the light	voluntary head shaking (0.3-3.0 Hz) while visually fixating a distant earth-fixed target (Chapter 5).	nominal gaze stability below 1.0 Hz, rapidly degrading between 1-2.5 Hz.

(continued on next page)

Table 3.1 - Formal experiments (continued).

Test		Method	Effects of "Torso Rotation"
1.9	Gaze stability in the dark	voluntary head shaking in the dark (0.3-3.0 Hz) while keeping eyes on imagined earth-fixed target (Chapter 7).	decreased velocity gain (eye vel./head vel.) similar *across all frequencies tested.*
1.10	Head shaking amplitude	voluntary head shaking in the light (0.3-3.0 Hz), trying to maintain a constant peak-to-peak amplitude of head movement at all times (Chapter 6).	about 15% increase in head shaking amplitude (1.0-2.0 Hz).

* Watt *et al.* 1989 (13)

Numbers in parentheses correspond to references to testing methods. Some have been used as is, while others have been slightly modified.

Table 3.2 - Preliminary results ($n < 4$).

Test		Instructions	Effects of "Torso Rotation"
2.1	Constant velocity rotation	stare straight ahead during constant velocity rotation in the dark (14).	VOR gain extrapolated to onset or end of rotation was decreased by about 15%. Different "stare" strategies were used resulting in inconsistent time constant values .
2.2	Circularvection	stare at infinity facing a dome rotating at constant velocity and rotate a crank matching speed of apparent self-motion (15).	about 50% decrease in perceived self-motion.
2.3	Heel-toe walking	walk straight ahead, eyes closed one foot directly in front of the other.	increased sway, extremely difficult task to perform immediately after TR.
2.4	Parallel swing	maintain upright posture while standing on parallel swing eyes closed with feet on 10 cm thick foam.	essentially impossible to do after TR.
2.5	Dynamic posture perturbations	maintain upright posture following fore-aft perturbation by sudden start of treadmill.	increased fore-aft sway after TR, both in the eyes open and eyes closed conditions.
2.6	Hopping frequency	hop up and down eyes closed (16).	no effects.
2.7	Voluntary saccades	make voluntary saccades under 3 conditions: -room light -red light -darkness	no effects.
2.8	Head step rotations	point head at targets after closing eyes.	overshoot of target.

Numbers in parentheses correspond to references to testing methods. Some have been used as is, while others have been slightly modified.

ALTERNATIVE FORMS OF TR

What are the critical features of TR that cause the greatest changes? To address this question, an evolving series of experiments were performed involving self-generated, rhythmical movement about different axes and requiring different combinations of eye, head and body movement. In some cases, two methods were used in the same 30 minutes conditioning period, with subjects alternating between them every 1-2 minutes. In other cases, controlled motor activity was alternated with a conditioning method. The results of all these experiments are compiled in Tables 3.3 and 3.4. At least nine subjects were tested with each method. In summary, these results suggest that *any type* of prolonged, voluntary eye and head movement requiring vestibular suppression will lead to temporary vestibular deficits and to some level of motion sickness.

DURATION OF TR

Subjectively, the effects of TR build up gradually and are sufficient at 30 minutes to use that duration as a standard. What is the actual time course of self-induced vestibular suppression, however? TR was performed for 6 different durations, from 2 to 64 minutes in 2^n increments. Two subjects took part, one performing TR with increasing durations, and one the reverse. Two independent measures of vestibular function were obtained from each subject at each session (tests 1.2 and 2.8 of Tables 3.1 and 3.2). VOR gain began to decrease within minutes of starting TR and was continuing to decline one hour later. Furthermore, as VOR gain fell, head overshoot increased in the second test.

Table 3.3 - Alternative forms of "Torso Rotation".

A- The different modes of stimulation and their effects.

Method name	Stimulus				Effects		
	Head mvts	Orient. re "g" vector	Torso mvts	Eyes open/ closed	Motion sickness	Gaze instability	Postural instability
3.1 Figure 8	Y P R	changing	yes	open	severe	Y P R	yes
3.2 Zig-zag	Y P	changing	yes	open	moderate	Y	yes
3.3 Yaw (vert)	Y	along	yes	open	mild	Y	yes
3.4 Yaw (horiz)	Y	at 90°	yes	open	mild	Y	yes
3.5 Eyes closed	Y	along	yes	closed	mild	Y	yes
3.6 Roll (vert)	R	along	yes	open	mild	R	yes
3.7 Roll (horiz)	R	at 90°	no	open	mild	R	yes
3.8 Head & eyes only	Y	along	no	open	mild	Y	yes
3.9 Eyes only	--	--	no	open	none	no	no

Y=YAW, P=PITCH, R=ROLL

B- Instructions to subjects.

Method name	Instructions
3.1 Figure 8*	-sweep the eyes around a large "∞" figure printed on the wall. As the eyes sweep right, tilt head to right, and as the eyes sweep left, tilt head to left.
3.2 Zig-zag*	-sweep gaze back and forth between 2 vertical lines 130° to either side of straight ahead. At the same time, slowly pitch the head up and down from neck fully flexed to neck fully extended.

(continued on next page)

Table 3.3 - Alternative forms of "Torso Rotation" (continued).

B- Instructions to subjects (continued).

Method name		Instructions
3.3	Yaw (vert) «standard TR»	-stand with feet 30 cm apart and arms crossed in front of body. -using the auditory cue for timing, sweep gaze back and forth between 2 fixed targets located 130° to either side of straight ahead, at 0.7 cycles per second.
3.4	Yaw (horiz)*	-stand with feet 30 cm apart and arms crossed in front of body, *then bend forward at the waist as close to 90° as possible.* -using the auditory cue for timing, sweep gaze back and forth between 2 fixed targets located 130° to either side of straight ahead.
3.5	Eyes closed	-stand with feet 30 cm apart and arms crossed in front of body. -*memorize the position of the 2 targets* located 130° to either side of straight ahead. -*close eyes*, and using the auditory cue for timing, sweep gaze back and forth between the *imagined* targets.
3.6	Roll (vert)*	-stand with feet 30 cm apart and arms crossed in front of body, *then extend neck as far as possible* and hold gaze on target on ceiling. -using the auditory cue for timing, rotate torso back and forth as if performing standard TR.
3.7	Roll (horiz)*	-stand with feet 30 cm apart and arms crossed in front of body, *and hold gaze on target directly in front of head.* -using the auditory cue for timing, *roll head rhythmically from side to side*, tilting about 45° to either side.
3.8	Head & eyes only*	-stand with feet 30 cm apart and arms crossed in front of body. -using the auditory cue for timing, *and rotating the head only*, look alternatively at the target located 90° to your right and the target located 90° to your left, at 0.7 cycles per second.
3.9	Eyes only	-*sit with head immobilized* by a custom-molded dental bite. -using the auditory cue for timing, *and moving only the eyes*, look alternatively at the target located 50° to your right and the target located 50° to your left, at 0.7 cycles per second.

* Watt *et al.* 1989 (13)

	PRT	VVIT	AHM (seated)	AHM (standing)	Yaw (horiz)	Yaw (vert)
Figure 8	√			√		√
zig-zag	√					
Yaw (vert)	√	√	√		√	

PRT= paper repositioning task (move 4 papers, one at a time, from one edge of floor to other, in same order, always facing forward).

VVIT= visual-vestibular interaction test (adapted from 17; locate randomly placed numbers in randomly numbered and lettered rows and columns).

AHM (seated)= active head movements while seated (pitch head 90° forward, to left, forward, to right, forward, etc.).

AHM (standing)= active head movements while standing (yaw/pitch left, upright, yaw/pitch right, upright, etc.).

Table 3.4 - Complex conditioning. Subjects were trained to alternate between two methods every 1-2 minutes for the duration of the conditioning.

SHORT-TERM ROLE OF VISION

Three different experiments have been carried out to look at the role of visual inputs *during* and *after* TR. If TR was performed eyes open or eyes closed, the amount of perceived gaze instability experienced afterwards was essentially the same, demonstrating that vision is not necessary for reduction in VOR gain, as reported previously by Melvill Jones *et al.* (4). To investigate the role of vision in the 20 minute recovery from TR, standard TR was followed by 20 minutes of controlled motor activity with eyes closed. Postural instability and motion sickness followed their normal time courses, gradually disappearing within the nominal 20 minutes. However, upon opening the eyes, substantial gaze instability remained, showing that the short-term recovery occurs independently for the different systems affected by TR. The same results were obtained regardless of the presence or absence of vision *during* the conditioning.

RECOVERY FROM TR IN THE ABSENCE OF VISION

Standard TR was carried out for 30 minutes, preceded and immediately followed by rapid VOR gain measurements. As expected, VOR gain dropped substantially after TR. The subject then remained in total darkness for six hours. During that time, ad lib motor activity was encouraged and the subject was kept alert by conversing with others in the room. As described previously, postural stability recovered rapidly within tens of minutes. At the end of the six hours, another test of VOR function was carried out and it was found that VOR gain had recovered by about 75-80%.

CONCLUSION

Standard TR has a generalized effect on many aspects of vestibular function. Other types of repetitive movement that also require temporary suppression of vestibular reflexes can produce similar effects. Larger changes are produced by longer durations of TR. Vision seems to play a minor role, other than assisting in the rapid recovery of gaze stability immediately after TR.

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Adaptation to Motion Sickness does not Correlate with Changes in VOR Gain.

INTRODUCTION

Motion sickness is an unpleasant and sometimes debilitating syndrome that has been recognized for thousands of years (see 1 for review). It consists of a wide variety of signs and symptoms including not only nausea and vomiting but also pallor, cold sweating, general malaise, stomach awareness and discomfort, increased salivation, belching, flatulence, yawning, headache, drowsiness, mental confusion, depression and apathy. Different combinations of the above can occur in any particular individual. Environments provocative of motion sickness are also quite varied, including ships, airplanes, cars, amusement park rides, rotating rooms (2), flight simulators (3, 4), parabolic flight (5) and space flight (6). Other situations involving self-generated movement can also be quite provocative: mal de débarquement (7, 8) and walking around while wearing reversed-vision spectacles (9, 10), etc.

In an effort to bring together the scattered knowledge in the motion sickness field, Reason proposed the sensory conflict theory (11). According to this "unifying" model, motion sickness results from a mismatch between the multiple sensory inputs generated by the environment and the ones expected by the brain. Reason's theory was a major step forward in that it brought together a very large amount of knowledge that sometimes seemed contradictory. Not surprisingly, it does have its limitations, the most important one being its lack of description of which anatomical structures or physiological systems might be involved, making it essentially impossible to test experimentally. This reflects the general lack of knowledge of the mechanisms underlying motion sickness. Even the presence of a brainstem vomiting center is still debated (12-16). The only point on which all seem to agree is that an intact vestibular system has to be present, otherwise the person (or animal) will not be susceptible to motion sickness (17 - 19).

Another aspect of motion sickness that has been known for thousands of years is that upon prolonged or repeated exposure to a provocative environment, the signs and symptoms eventually disappear. This process, variously called adaptation, habituation or desensitization, has been observed in all of the provocative environments known to date. According to Reason's model (11), adaptation would be the outcome of the brain updating its internal maps of expected sensory combinations after having been sufficiently exposed to the provocative environment. Here also, the theory provides no information about the neural circuitry that might be involved (20, 21). It also leaves open the possibility of contributions by other, quite different mechanisms. Reason's model argues for a very specific, non-transferable type of protection. Others have noted that a more general, transferable adaptation also occurs (22).

For several years, we have been searching for physiological changes occuring during adaptation to motion sickness. In particular, we have been studying the effects of "Torso Rotation" (TR), an unusual motor strategy that produces an acute, reversible change in human vestibular function, possibly through excessive suppression (23). A single, short exposure to TR results in perceptual illusions, gaze and postural instability, and motion sickness. Vestibulo-ocular response (VOR) gain is also decreased for up to 20 minutes. With repeated exposure to TR, motion sickness symptoms disappear and gaze instability seems to be decreased. Is this because the transient decrease in VOR gain is also reduced?

This work has been presented elsewhere in the form of preliminary results (24) and as an abstract (25).

METHODS

TORSO ROTATION

The term "Torso Rotation" has been used to describe a motor strategy in which the head is fixed voluntarily to the torso during active, self-generated movement (26 and Chapter 3). Over time, this will result in motion sickness in many individuals. To standardize the method, and to enhance its effect, we have used an exaggerated form of torso rotation in these experiments.

The technique consisted of the following: subjects were trained to sweep their eyes back and forth between 2 visual targets located 135° left (-) and right (+) of straight ahead at eye level. A 1.4 Hz sound cue (one click at each target) resulted in a 0.7 Hz eye, head and body oscillation. To reach the targets, simultaneous movements of the eyes(±135°), head (±90°) and torso (±45°) were required. Subjects performed TR continuously for 30 minutes, while being watched constantly by a trained observer.

CONTROLLED MOTOR ACTIVITY

Normal motor activity after TR also had to be standardized, to ensure that all subjects recovered in a reasonably controlled fashion. To achieve this goal, a simple method was designed that forced a substantial amount of coordinated eye, head and body movements in all 6 degrees of freedom. The subject stood inside a small cupboard with 5 rows of 4 random numbers (range 0-999) on each wall (Figure 4.1). The task was to locate and reorient to a pre-selected sequence of these numbers as indicated by an observer. This task was performed continuously between the 3 post-TR tests.

Figure 4.1 Controlled motor activity consisted of retreiving numbers from the walls of a small cupboard. Each wall had five rows of 4 random numbers (range 0-999).

MOTION SICKNESS QUESTIONNAIRE

Motion sickness level was evaluated using a custom designed questionnaire in which subjects had to rank their symptoms according to a "none", "mild", "moderate" or "severe" scale as each was read off by an observer, who also noted any pallor or cold sweating (Figure 4.2). At the end of the questionnaire subjects were asked to give an index of their overall discomfort level (adapted from 27), ranging from 0 to 20 where 0 = normal and 20 = retching / vomiting. Before the experiment, all subjects were carefully instructed as to the meaning of each symptom, and how to estimate overall discomfort level.

MEASUREMENT OF VOR GAIN

Vestibulo-ocular response (VOR) gain was measured using whole body step rotations in the dark (modified from 28). A complete description of the test has been published previously (26). In short, subjects were secured into a manually operated rotating chair by means of upper-arm clamps and a custom-molded dental bite (Figure 4.3). They were rotated in the dark pseudo-randomly to either 10, 20 or 30° left or right of straight ahead, while asked to follow their mental image (not afterimage) of a distant earth-fixed target. The light then returned, and they had to refixate the real target if necessary. After a 5 second rest period, the sequence was repeated until a total of 24 rotations were completed. Total test duration was 4 minutes. Head movements were measured using a high precision potentiometer mounted on the axis of rotation of the chair. Eye movements were measured using conventional electro-oculography (DC to 200 Hz). The sequence of rotations, lights on/off and data collection were under computer control.

Are any of the following signs or symptoms of motion sickness present?

	none	mild	moderate	severe
cold sweating	[ ]	[ ]	[ ]	[ ]
pallor	[ ]	[ ]	[ ]	[ ]
stomach awareness	[ ]	[ ]	[ ]	[ ]
stomach discomfort	[ ]	[ ]	[ ]	[ ]
malaise				
nausea	[ ]	[ ]	[ ]	[ ]
vomiting/retching	[ ]	[ ]	[ ]	[ ]
salivation	[ ]	[ ]	[ ]	[ ]
belching	[ ]	[ ]	[ ]	[ ]
yawning	[ ]	[ ]	[ ]	[ ]
flatulence	[ ]	[ ]	[ ]	[ ]
headache	[ ]	[ ]	[ ]	[ ]
subjective warmth/flushing	[ ]	[ ]	[ ]	[ ]
drowsiness	[ ]	[ ]	[ ]	[ ]
mental confusion	[ ]	[ ]	[ ]	[ ]
apathy	[ ]	[ ]	[ ]	[ ]

overall discomfort level (0-20):_____

Figure 4.2 This questionnaire was used to evaluate the signs and symptoms of TR-induced motion sickness. Subjects had to rank themselves verbally, as the experimenter was systematically going through the list.

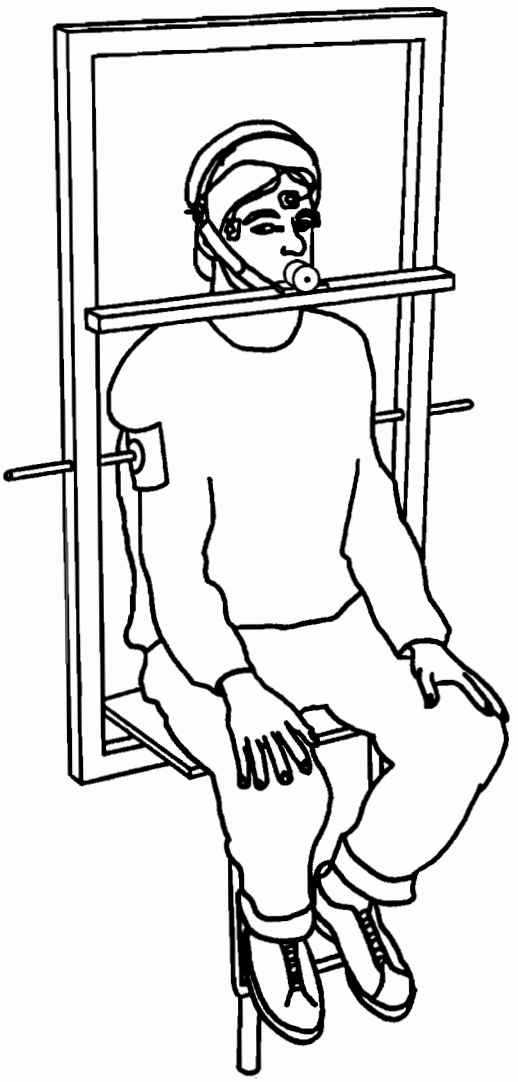

Figure 4.3 For VOR testing, subjects were secured into this manually-operated rotating chair by upper-arm clamps and a custom molded dental bite. A computer-controlled LED panel located at the back of the chair indicated when and where to rotate the subject.

The net VOR gain (Figure 4.4) was calculated as the ratio of the angle covered by the eyes during the rotation (A) over the angle they should have covered, as defined by eye position after the refixation saccade in the light. Any saccades occurring during the rotation (C) were identified using reconstructed gaze traces (eye re head plus head re space) and subtracted from the total displacement (A), yielding the smooth phase VOR gain ((A-C)/B). In general, few compensatory saccades were used by our subjects.

TESTING SCHEDULE

Six subjects (5 male and 1 female) with no histories of inner ear problems participated in 3 separate but related experiments, each of which lasted 7 days. To prevent transfer of adaptation or other ordering effects, each subject performed the 3 experiments in a different order, with at least 3 weeks between the end of one and the beginning of the next. On each day, subjects were tested 4 times: before TR ("BE"), immediately after TR ("IA"), 10 minutes after TR ("10") and 20 minutes after TR ("20"). Post-TR, subjects performed controlled motor activity between tests. The 3 experiments were: a) assessment of motion sickness level; b) VOR experiment and c) VOR control. All experiments had been approved a priori by a committee on human ethics.

The assessment of motion sickness level experiment consisted of completing a motion sickness questionnaire before and 3 times after TR. The VOR experiment consisted of measuring VOR gain before and 3 times after TR. The VOR control was essentially the same as the VOR experiment, except that TR was replaced by 30 minutes of quiet sitting.

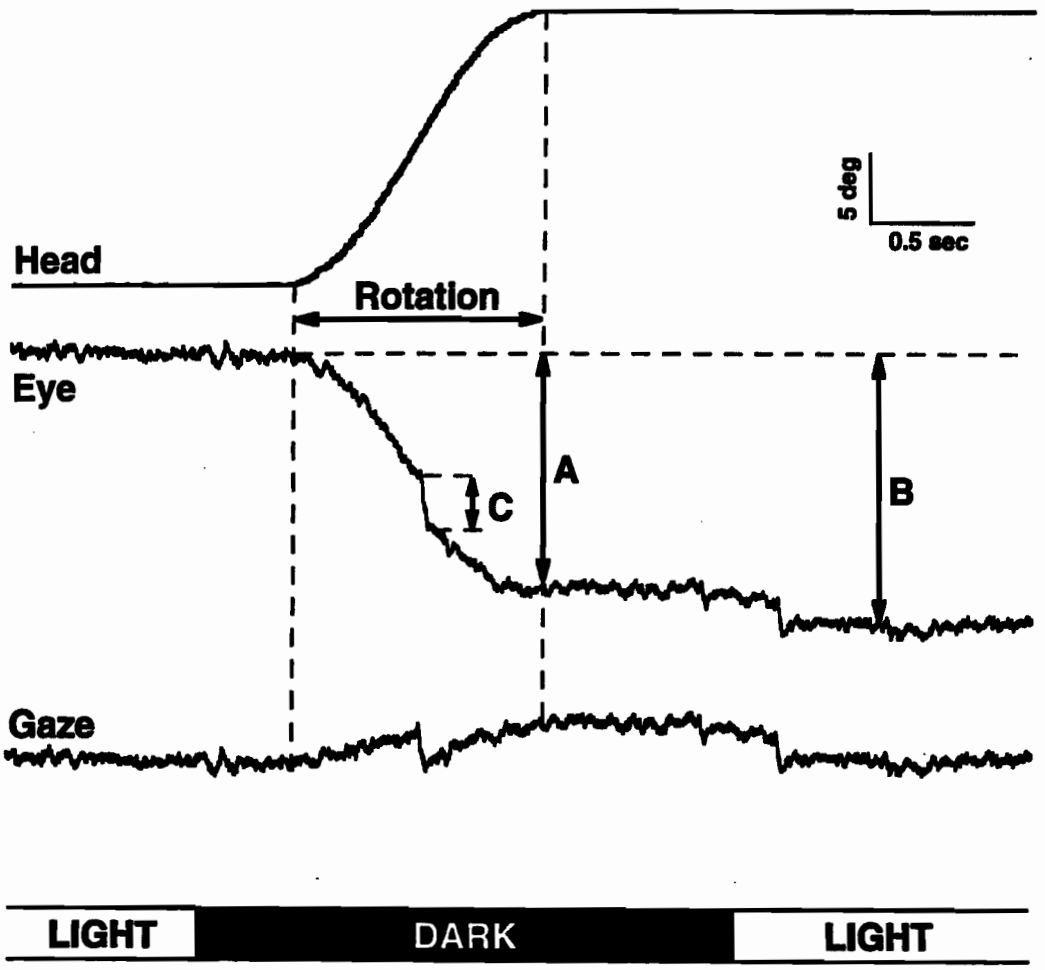

Figure 4.4 VOR gain determination. Eye and head traces represent raw data obtained during one step rotation before "Torso Rotation." Net VOR gain was defined as the angle covered by the eyes during the rotation in darkness (arrow A) divided by the angle they should have covered represented by arrow B, at a point where the subject is actually fixating the target in the light. Saccades (arrow C) were identified using the gaze trace (eye re space). Smooth phase VOR gain was defined as the ratio (A-C)/B.

RESULTS

MOTION SICKNESS

TR proved to be a very provocative stimulus for some participants. In the worst case, a subject rated himself 18/20 on the overall discomfort level scale at the "10" test on day 1. Included in his signs and symptoms were severe cold sweating, stomach discomfort, flatulence, malaise and nausea, moderate pallor, mental confusion and apathy, and mild salivation, belching, headache, flushing and drowsiness. Note that peak motion sickness level was always observed at the "10" and not the "IA" session. As shown previously, subjects had to move around with altered vestibular function before motion sickness symptoms appeared (26). Fortunately, not all subjects reacted so vigorously. The range of responses on day 1 was 5 - 18 (mean = 11.5).

The effect of repeated exposure to TR on motion sickness level is shown in Figure 4.5. The group average (± S.D.) overall discomfort level declines over 3-4 days. Interestingly, subjects reported that adaptation to TR carried over to other provocative environments such as cars, buses, etc. An exponential curve was fit to the data using the least squares method (R^2 = 0.989). Most of the variability was due to expected differences in susceptibility between subjects.

CHANGES IN VOR GAIN

VOR gain values measured in one subject on day 1 are shown in Figure 4.6. This is a different subject from the one referred to in the motion sickness section above. Each point in the figure represents the response to a single rotation. Much of the scatter is due to a relatively low signal to noise ratio at the smallest rotation angles. Before TR, VOR gain was close to unity. During test "IA", the subject consistently and significantly ($P < 0.001$, paired t-test)

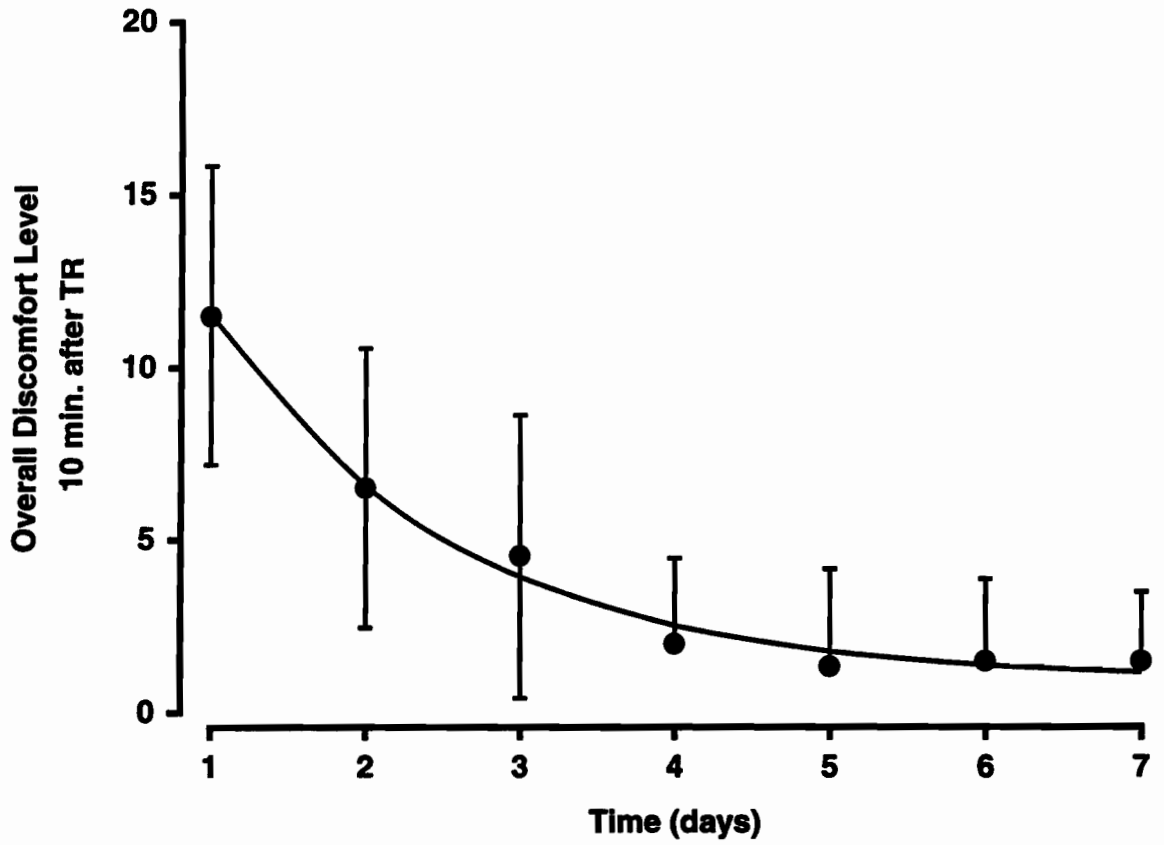

Figure 4.5 Time course of adaptation to TR-induced motion sickness. Mean ± S.D. of 6 subjects. Exponential curve fit with a time constant of 1.6 days (least squares method, $R^2 = 0.989$).

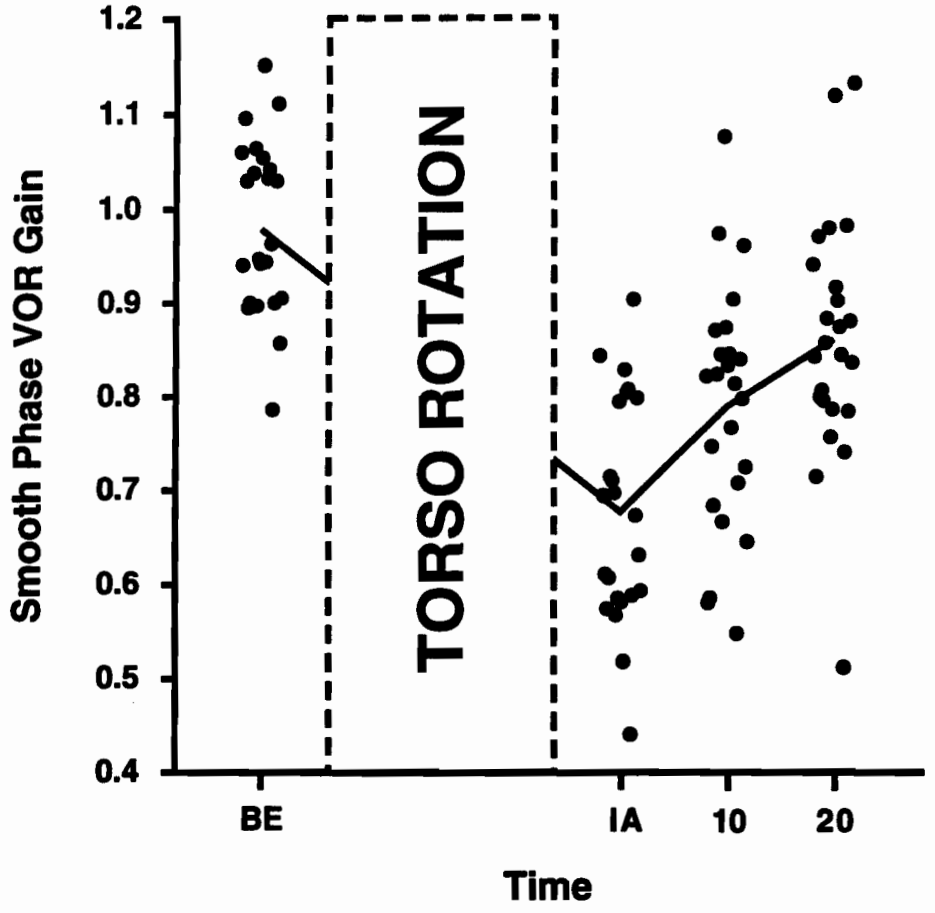

Figure 4.6 Typical daily response to "Torso Rotation". Each point represents one rotation. Straight lines join the means of each test. "BE": before TR. "IA": immediately after TR. "10": 10 minutes after TR. "20": 20 minutes after TR. Immediately after TR, VOR gain was significantly reduced (paired t-test, $P<0.001$). Recovery was almost complete by the "20" test.

undershot the target at all rotation angles. This was true for all 6 participants. Paired statistics could be used because the pseudo-random sequence of rotations was identical for all testing sessions.

Results from the 6 subjects for each of the 7 days are presented in Figure 4.7 as mean smooth phase VOR gain (± S.E.M.) versus time. Each point represents the average of 144 rotations (6 subjects, 24 rotations each). Each day, "IA" VOR gain was significantly decreased ($P < 0.01$). Furthermore, there was no significant difference in the amount of suppression from day to day (paired t-test of the difference between "BE" and "IA", comparing each possible pair of days).

To look for possible changes in the daily recovery rate, data from Figure 4.7 were redrawn in Figure 4.8. This time, the 7 days were superimposed and zeroed relative to the daily "IA" session. There was no systematic trend from one day to the next. This figure suggests that the rate of recovery was therefore the same each day, at least within the temporal resolution of our measurements.

Compensatory saccades (Figure 4.4, "C") were not observed consistently during VOR testing. In fact, only 3 of our 6 subjects showed any at all. Overall, the transient daily changes in VOR gain were not accompanied by changes in saccadic gain, defined as ratio C/B in Figure 4.4 (Figure 4.9). Furthermore, as they adapted to motion sickness, subjects did not significantly increase their saccadic gain after TR (paired t-test of the difference between each post-TR session (i.e. "IA", "10" and "20") and their respective "BE", see Figure 4.9).

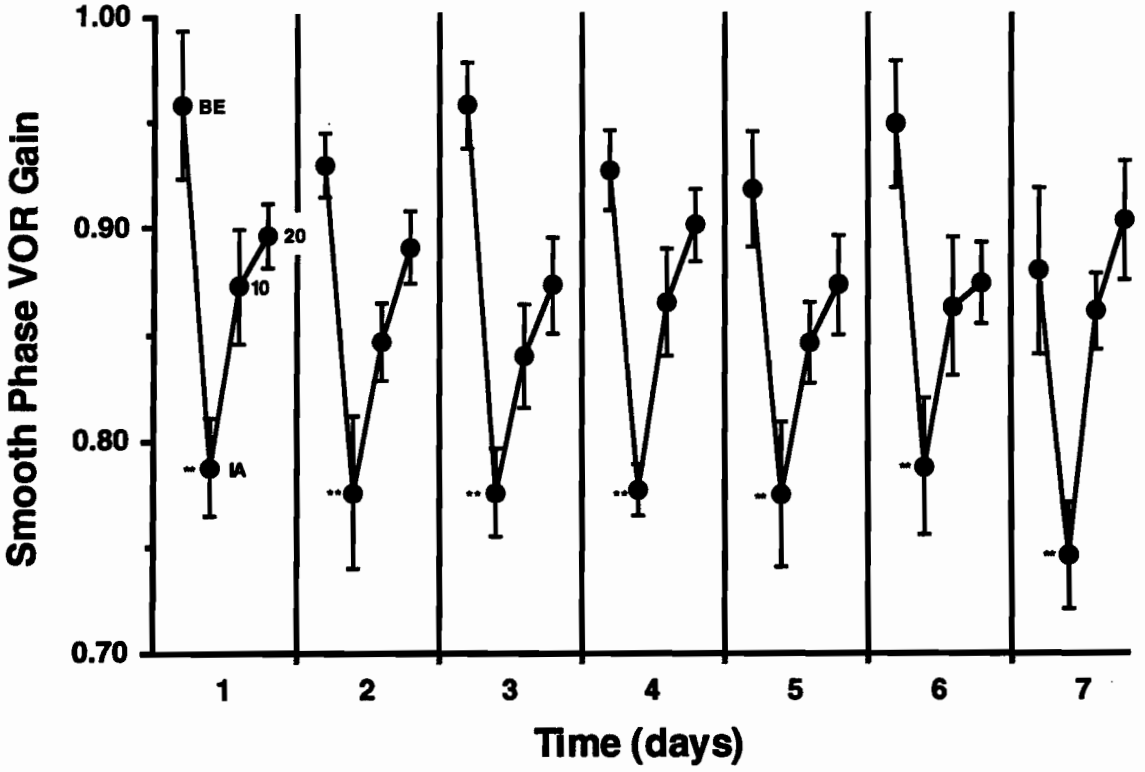

Figure 4.7 Effects of repeated exposure to TR on group mean VOR gain. Each point represents the mean ± S.E.M. of a total of 144 rotations, in 6 subjects. ** $P<0.01$, paired t-test relative to "BE" value. VOR gain was significantly lower each day immediately after TR, returning to normal in about 20 minutes. No long term trend was observed.

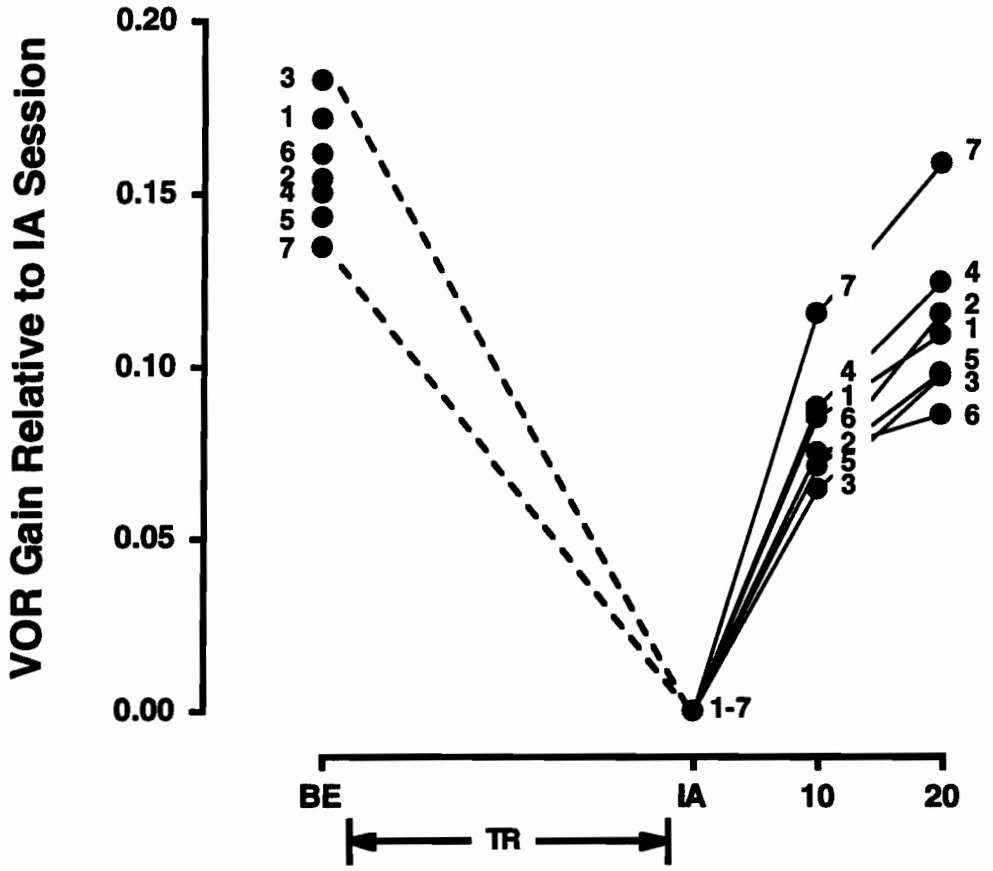

Figure 4.8 Comparison of the daily recovery rates. Data from Figure 4.7 have been replotted, superimposing the 7 traces after zeroing them relative to their respective "IA" point. Each point is labeled 1 - 7, corresponding to the day it represents. No systematic trend is evident in the recovery profile.

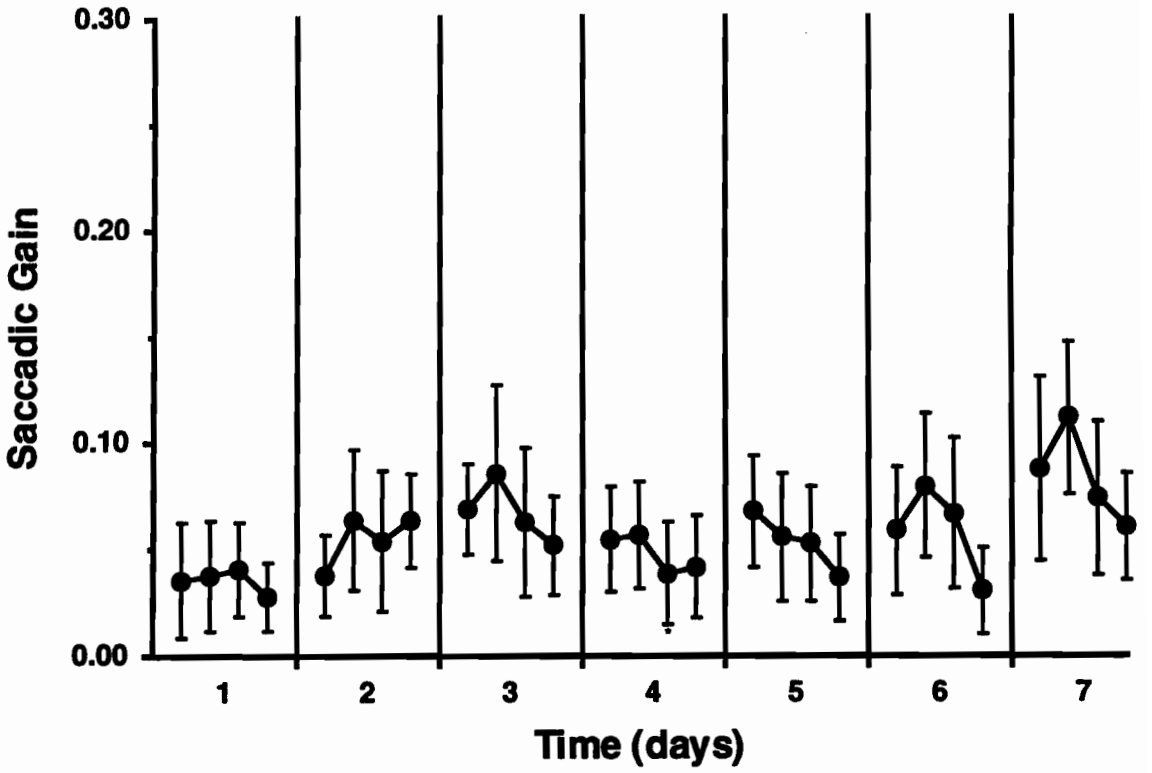

Figure 4.9 Effects of repeated exposure to TR on group mean saccadic gain. Each point represents the mean ± S.E.M. of a total of 144 rotations, in 6 subjects. * $P<0.05$, paired t-test relative to "BE" value. Unlike smooth phase VOR gain, saccadic gain was not systematically affected by a single session of TR. Repeated exposure to TR also did not affect the gain.

CONTROL EXPERIMENT

Figure 4.10 shows the time course of VOR gain measured on 7 consecutive days during the VOR control experiment. This experiment was identical to the "VOR experiment" (Figure 4.7), except that subjects did not perform TR. Subjects did not show short-term (single session) or long-term (7 days) effects of the step rotation testing method or of controlled motor activity on VOR gain. On day 5, "IA" was significantly *higher* (paired t-test, $P < 0.01$) than "BE", however.

DISCUSSION

It has been suggested that motion sickness might be related to or even caused by gaze slip, perhaps originating from an altered VOR gain. This explanation has been put forward mainly because altered VOR gain values have been measured in several provocative environments (e.g. 5, 9, 10, 29). According to this theory, adaptation to motion sickness during *prolonged exposure* to a provocative environment would result from a gradual return of VOR gain towards unity. Adaptation to *repeated exposure* would consist of a decreased tendency of the VOR to change in that environment. While little supporting evidence exists, Shupak et al. (30) have reported increased VOR gain at 0.01 Hz after adaptation to seasickness. However, this frequency is far outside of the normal range of head movements (31) and the semi-circular canals are known to respond as velocity transducers only in the range 0.1 - 5.0 Hz (32), so the functional significance of this change is unclear.

As an alternative to changes in slow phase eye movements, Segal (personal communication) has proposed that gaze slip might be decreased if the subjects' oculomotor strategies became more saccadic. This was based in part on work showing that some unilateral vestibular patients have the

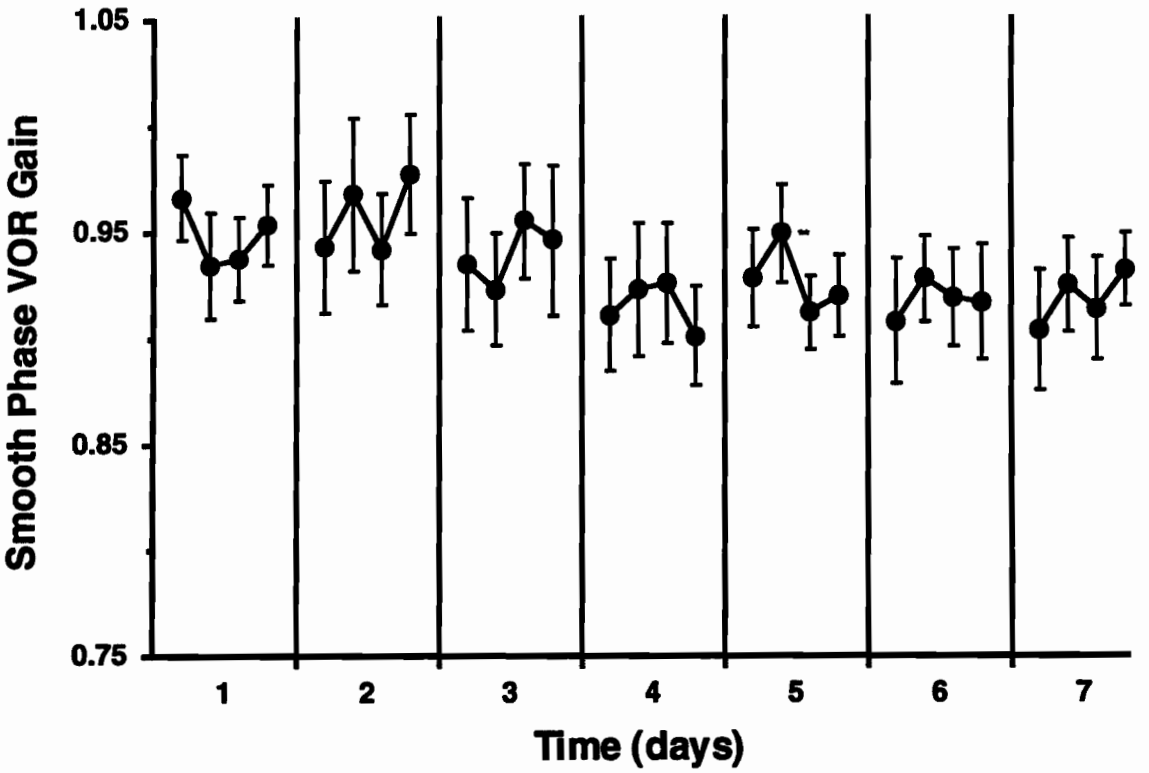

Figure 4.10 Control experiment: effects of repeated testing on group mean VOR gain. Each point represents the mean ± S.E.M. of a total of 144 rotations, in 6 subjects. ** $P<0.01$, paired t-test relative to "BE" value. VOR gain was not systematically affected by the testing method or the controlled motor activity performed between tests.

ability to compensate their slow phase deficit by increasing their use of compensatory saccades during horizontal step rotation testing in the dark (33). The same authors also showed the presence of compensatory saccades in some normals (34). Potentially, our subjects could also boost their "saccadic" gain.

Confirming earlier subjective observations (26), repeated exposure to TR resulted in a progressive decrease in motion sickness signs and symptoms (Figure 4.5) and a subjective improvement in post-TR gaze stability. The time course of adaptation was similar to that reported in other provocative environments (6, 13, 16). However, despite the complete loss of susceptibility to motion sickness, the measured drop in VOR gain tended to be the same on each of the 7 days. Furthermore, the pattern of VOR recovery in the 20 minutes after TR also tended to remain constant. Saccadic gain, which was always very low, also remained essentially unchanged.

Therefore, it must be concluded that adaptation to TR-induced motion sickness is NOT a result of the VOR, or any neural circuitry that it reflects, becoming less susceptible to modification by TR. Nevertheless, gaze stability during rapid, voluntary head movements DOES appear to improve with repeated exposure, even though this can't be related to changes in the VOR. Perhaps another contributor to gaze stability is being substituted for the periodically unreliable vestibular reference. At least 3 other systems are available for compensation: vision (35), the cervico-ocular reflex (36-38) and predictive mechanisms (39, 40). Alternatively, the apparent improvement may be a high-level perceptual change, with no actual change in retinal image slip (41). These issues will be examined in the subsequent experiments (Chapter 5-8). By comparing the results of these different studies, we should be able to isolate which of these systems is responsible for the long-term

	Vision	Cervico-ocular reflex	Predictive mechanisms	Vestibulo-ocular reflex
Head Shaking (LT)	•	•	•	•
Head Shaking (DK)		•	•	•
Head and Torso Shaking (DK)			•	•
Passive Step Rotations (DK)				•

Figure 4.11 The experimental tests performed in this thesis and the neurophysiological systems that they may involve (see Chapters 4-8 for details). LT= with the room light on; DK= in total darkness.

improvement in gaze stability (Figure 4.11).

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Chapter 5

Gaze Stability during Voluntary Head Movements Improves with Adaptation to Motion Sickness.

INTRODUCTION

In the previous experiment (Chapter 4), repeated exposure to "Torso Rotation" (TR) resulted in a progressive decrease in motion sickness signs and symptoms and an apparent improvement in post-TR gaze stability during rapid, voluntary head movements. However, the measured drop in vestibulo-ocular response (VOR) gain and its pattern of recovery following TR were the same on each of the 7 days of testing. Thus gaze stability seemed to improve despite a consistently compromised VOR. This is not completely surprising, since partial gaze stability recovery after bilateral labyrinthectomy has also been shown in humans (1, 2). The actual adaptive strategy seemed to vary from one patient to the next, however.

The goal of this experiment was to determine if a measurable improvement in post-TR gaze stability actually occurs with repeated exposure, using a method that allows the subjects access to all possible means of compensation (see Figure 4.11), namely head shaking in the light. Later experiments will address how this improvement occurs.

This work has been presented elsewhere as an abstract (3).

METHODS

TORSO ROTATION

TR consisted of self-generated rhythmical movements in which subjects swept their gaze back and forth at 0.7 Hz between 2 visual targets located 135° left and right of straight ahead, continuously for 30 minutes. Further descriptions of the technique have been published elsewhere (4 and Chapter 3).

CONTROLLED MOTOR ACTIVITY

Motor activity after TR was also standardized, to ensure that all subjects recovered in a reasonably controlled fashion. To achieve this goal, a simple task consisting of reorienting to a series of random numbers on the walls of a small cupboard was designed (Chapter 4). This task was performed continuously between the 3 post-TR tests.

HEAD SHAKING TEST

Overall gaze stability was assessed during voluntary, side-to-side head shaking in the light. Five male subjects were asked to fixate a distant (4 meters), earth-fixed visual target while following a series of audible beeps that caused them to sweep their head shaking frequency from 3.0 to 0.3 Hz. They were also carefully instructed to maintain a constant amplitude of head movements (about ± 15°). One other male subject performed the same experiment, but sweeping up in frequency rather than down. Although successful, it proved to be far more difficult to maintain a reasonably constant amplitude of head shaking under the latter conditions.

Eye position was measured using conventional electro-oculography (DC to 200 Hz). Head position was measured using a goniometer attached to a head band system, with a demonstrated resolution of ± 0.5° (Figure 5.1). Eye and head position signals, low-pass filtered at 200 Hz for anti-aliasing, were sampled at 800 Hz/channel, directly into a computer. EOG signals were calibrated by comparing eye movements to known head movements during very low frequency movements.

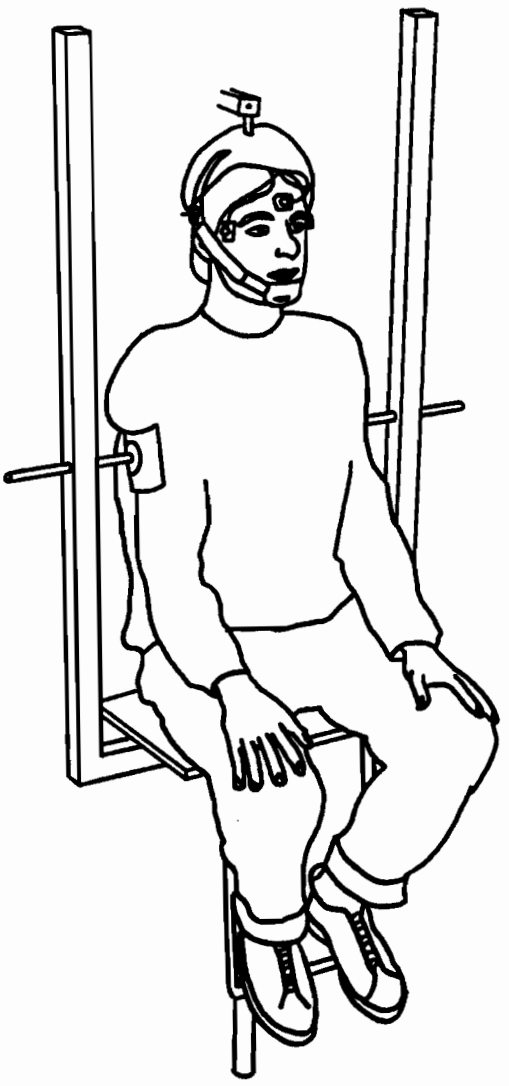

Figure 5.1 The chair used for step rotations in the previous Chapter was locked in place and used as a whole body restraint. Only the head was free to move. Head movements were measured using a high resolution head band / goniometer system.

DATA ANALYSIS

The analysis method used in this experiment was designed to overcome a series of limiting problems, both technical and physiological, which are described below.

Head movement patterns were never truly sinusoidal. Furthermore, visual inspection indicated that their shape changed with frequency, from close to sinusoidal at the higher frequencies to essentially triangular at the low end. In some cases during the "IA" test, the peak to peak head displacements were close to the subject's oculomotor range limit and outside the linear range of EOGs. Together, these factors prevented us from using classical head shaking analysis methods (5-9).

The method we adopted (velocity gain analysis) was carried out as follows, using data acquisition, filtering and analysis software written by the author. Head and eye position signals were calibrated, filtered, differentiated and decimated down to 100 samples/sec. using digital signal processing techniques (10). Gaze position (eye re space) was computed by adding the original head and eye position traces. Head, eye and gaze position as well as head and eye velocity traces were then displayed together on a computer screen. Consecutive cycles of head movement were identified by placing a vertical cursor on an easily identifiable point in each cycle such as the peak velocity. The frequency of a given cycle was defined as the inverse of its duration in seconds. It should be noted, however, that using the term *frequency* is arbitrary in this context since voluntary head movements are never sinusoidal. Cycles of data were then pooled in frequency bins 0.2 Hz wide. For each frequency bin containing more than one cycle of data, a plot of instantaneous eye velocity versus instantaneous head velocity was created. A linear regression line was fit to the data, the slope of which was the velocity

gain. A coefficient of determination (R^2), indicative of the goodness of fit, was also calculated for each bin. Note that a slope of minus one and an R^2 of plus one on such a plot would be indicative of perfect target holding by the subject over the given frequency range of head movements.

These plots provided much information regarding subject performance and gave reproducible results. Phase lead or lag of the eye (re head) would cause the data to form an ellipse, not a straight line. Saccades would appear as sharp spikes superimposed on the straight line. Velocity saturation, a potential physiological limit when eye velocity exceeds 350°/sec (11), would be seen as non-linearities at the extreme ends of the curve. A subject exceeding his oculomotor range or the linear range of EOGs would produce a curve with non-linearities around 0°/sec. Backlash in the head-attached goniometer would also disrupt the linearity of the signal around 0°/sec. In contrast, a non-sinusoidal profile of head movements would not affect the measurements. Different amplitudes of head shaking at the same frequency would simply shorten or lengthen the curve without affecting its linearity or slope, as long as the subject stayed within his oculomotor range and the linear range of EOGs and did not reach the physiological velocity saturation of the gaze control system.

This latter feature was most useful, since an unexpected complicating factor was noticed during the analysis: each day immediately after TR ("IA") subjects were systematically moving their heads more than before TR ("BE", see Chapter 6). In turn, these variations in amplitude caused systematic changes in the velocity profile of the signals, shortening or lengthening the eye velocity versus head velocity curve. We therefore had to use an analysis method that could compare results obtained at the same frequency but at systematically different amplitudes. In some subjects, the peak velocities

reached at the highest frequency were near 400°/sec. However, no velocity saturation was observed on these plots, therefore allowing comparisons between all data sets.

TESTING SCHEDULE

The testing schedule designed for the previous experiment was also used here (Chapter 4). In short, subjects were tested on 7 consecutive days, a period long enough to cover adaptation to TR-induced motion sickness and a little beyond. Each day, 4 measurements were obtained: before TR ("BE"), immediately after TR ("IA"), 10 minutes after TR ("10") and 20 minutes after TR ("20"). Six subjects with no history of inner ear problems took part in the experiment, which had been approved a priori by a committee on human ethics. Three of them had participated to the experiments described in the previous Chapter.

RESULTS

PATTERN OF HEAD SHAKING

Data from a complete head shaking session in one subject before TR are shown in Figure 5.2. The top 2 traces represent raw data. Gaze position, head velocity and eye velocity were calculated as described under methods. At the higher frequencies, gaze stability was good but not perfect. At the lower frequencies, the eyes were even closer to the target. No saccades are present in this example, and were seen only rarely in all of the data we collected. When present, they were identified using vertical cursors, and data points between the cursors were rejected.

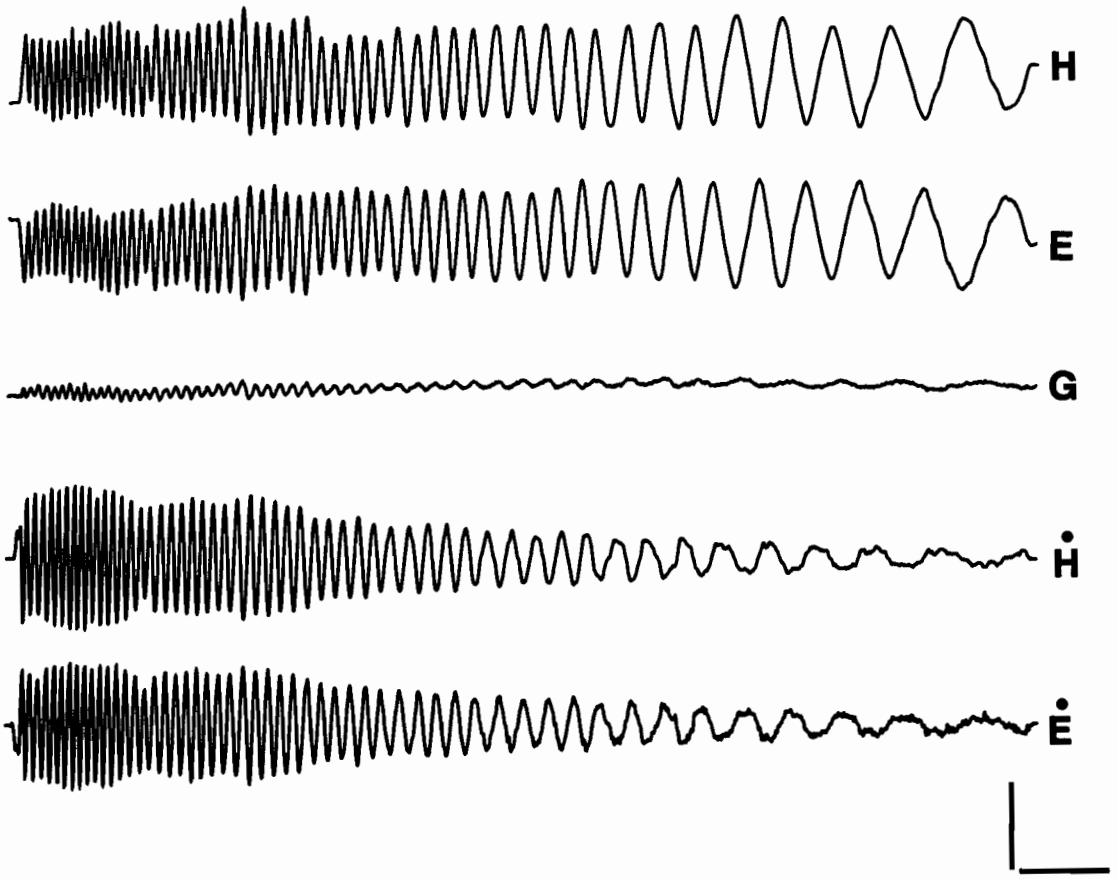

Figure 5.2 A complete head shaking session before "Torso Rotation". Legend: head position (**H**); eye position (**E**); gaze (eye re space) position (**G**); head velocity ($\dot{\mathbf{H}}$); eye velocity ($\dot{\mathbf{E}}$). Vertical scale represents 30° for the position traces and 300°/sec for the velocity traces. Horizontal scale represents 5 seconds.

MEASUREMENT OF VELOCITY GAIN

Figure 5.3 illustrates the velocity gain analysis method; instantaneous eye velocity has been plotted against instantaneous head velocities for the frequency bin 2.6 - 2.8 Hz. The data were taken from the set shown in Figure 5.2. The slope of the first order linear regression is -0.88, i.e. the eye movements are not perfectly compensating for the head movements. The linearity of the signal is quite good and noise is low, resulting in an R^2 of 0.990. The points around 0°/sec are not quite on the regression line, however. As described, multiple factors could be contributing to this small effect, including a small amount of slippage of the head band / goniometer system when the head changes direction, the fact that the differentiated EOG signal becomes noisy when eye position is not changing very quickly, or a very small phase shift.

PHASE SHIFTS

The combination of differentiated signal quality, sampling rate and head shaking frequency meant that phase shifts greater than 8° could be easily identified by this technique as a typical ellipse-like distortion of the curve. We did not observe such a behavior throughout the analysis of the results, showing that for these experimental conditions, significant phase shifts are not present in normals, or induced by TR, over the frequency range tested.

VELOCITY GAIN AS A FUNCTION OF FREQUENCY

Analyzed results from one subject on day 2 are shown in Figure 5.4. Velocity gain has been plotted as a function of frequency, and the 4 tests have been superimposed to allow comparison. Before TR, the gain was close to unity at all frequencies tested, and gaze stability was therefore very good.

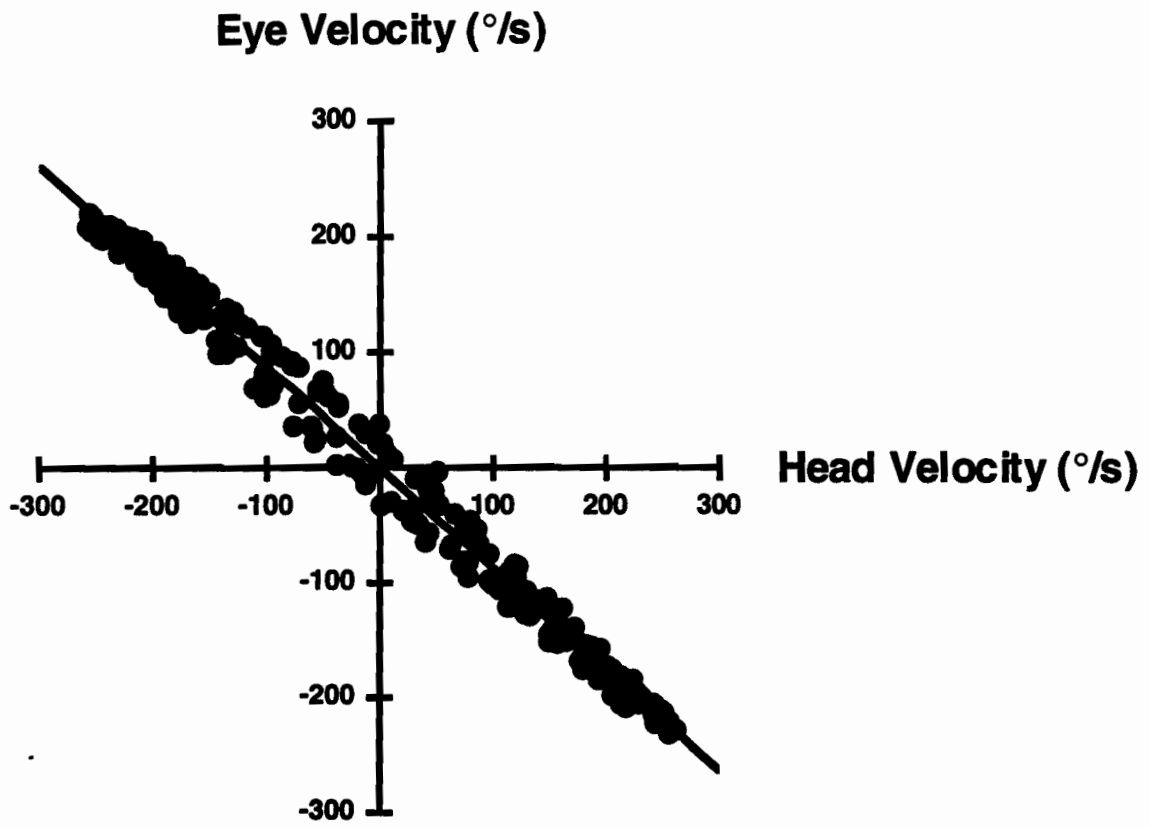

Figure 5.3 Velocity gain evaluation. For each frequency bin (in this case 2.6-2.8 Hz), instantaneous eye velocity was plotted against instantaneous head velocity. The slope of the linear fit (least squares method) defines the term "velocity gain". In this particular example, velocity gain is -0.88 (R^2 = 0.990).

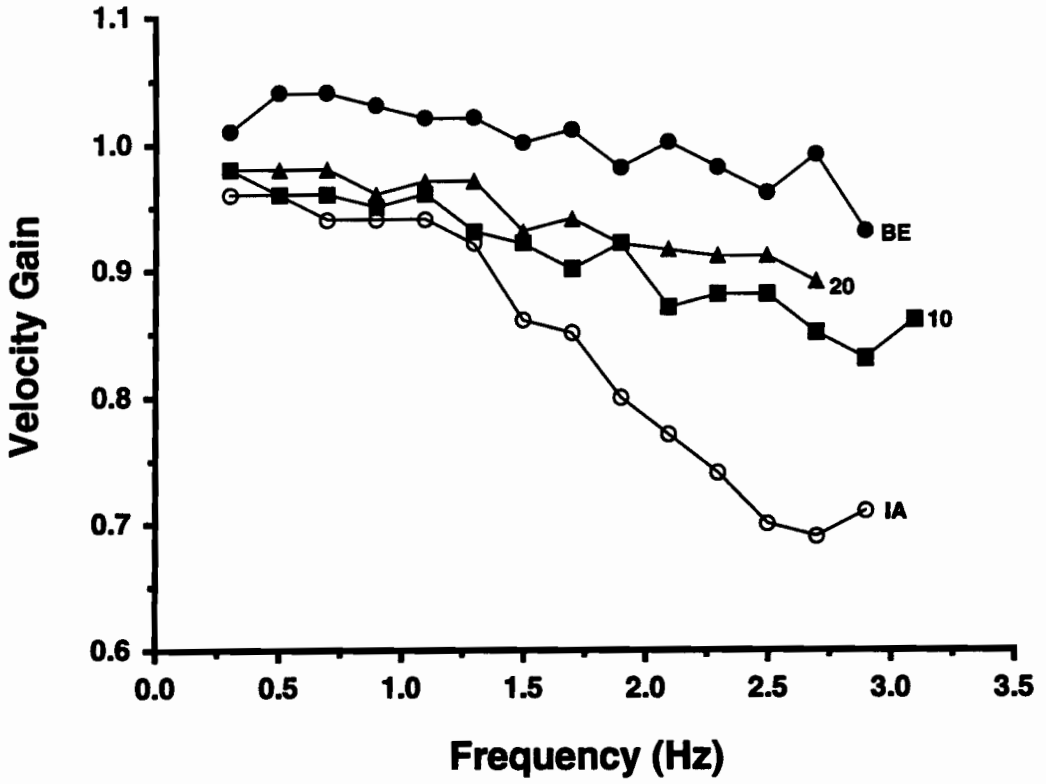

Figure 5.4 Frequency response curves for the four daily tests in one subject. Before TR ("BE"), velocity gain is close to unity at all frequencies, i.e. image slip is minimal. Immediately after TR ("IA"), the gain falls with frequency in the range 1.0 - 2.5 Hz. A large increase in gain is seen between "IA" and 10 minutes after the completion of TR ("10"). By 20 minutes post-TR ("20"), gaze control is most of the way back to normal.

After TR, the gain was greatly decreased, especially at the higher frequencies. As shown for the VOR elsewhere (Chapter 4), the response was almost back to normal in 20 minutes.

We were concerned that the mere presence of substantial gaze slip during the head shaking test could influence the results, i.e. immediately change the gain of the VOR (8, 12, 13). When we compared the frequency response curves of the single subject that did the sweep up test (see methods) to those of the rest of the group, there was no obvious difference. If there had been a significant influence of gaze slip on the results, we would have expected to see quite different curves since in the sweep down condition large amounts of gaze slip are experienced early during the test, but only towards the end in the sweep up condition. We therefore feel confident that gaze slip experienced during the test had no serious influence on our data. Note, however, that even if there was an effect of gaze slip on the data, it should be the same each day because the test was always performed exactly the same way. Thus, even though the curves shown in Figure 5.4 might be slightly distorted, this would not affect the conclusions drawn from this experiment.

COEFFICIENT OF DETERMINATION

The goodness of fit, as evaluated using the coefficient of determination (R^2, see methods), was always greater than 0.80 and most of the time greater than 0.97. These results show that the linear approximation of the eye versus head velocity relation is adequate to fully describe our data.

CHANGES IN VELOCITY GAIN WITH TIME

To allow comparisons between the adaptation to motion sickness results (Figure 4.5) and head shaking, it was necessary to reduce the data from a full frequency response curve to a single value per test. Data below 1

Hz were ignored because those data points were always close to unity, due to the dominant role of visual tracking in this frequency range (6, 14). The highest frequency considered was set by the highest frequency reached by all subjects during all tests, namely 2.0 Hz. To determine how well the subjects could keep their eyes on the target, a simple arithmetic mean of the velocity gain values was calculated for each subject over this range. Data shown in Figure 5.5 represent the time course of changes in the group mean velocity gain over the 7 days. The standard error bars represent inter-subject variability, i.e. we first averaged the data for each subject and then pooled them to calculate the group mean velocity gain and the standard error. Each day, the "IA" gains were always significantly lower ($P<0.01$, paired t-test) than "BE".

ADAPTIVE TIME CONSTANT

In Figure 5.6, each of the seven "IA" points from the previous figure have been re-plotted. There was a significant improvement in group mean velocity gain by the third day of testing ($P<0.01$). The gain never went back to pre-TR values, however. An exponential curve was also fit to the data (least squares method). It had a time constant of 2.3 days ($R^2 = 0.694$). The latter is a measure of the rate of improvement of gaze stability. Taking into consideration that a partly different group of subjects was used, this time constant is surprisingly similar to that of the loss of motion sickness susceptibility obtained in the previous experiment (1.6 days, see Figure 4.5).

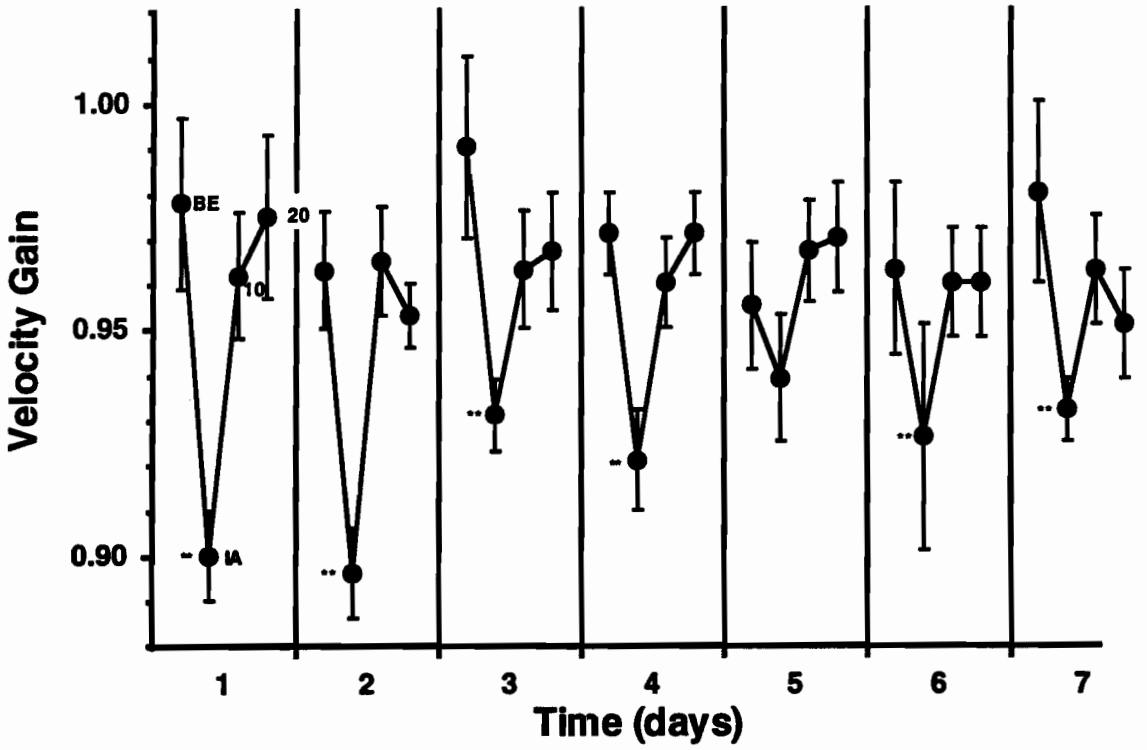

Figure 5.5 Effects of repeated exposure to TR on group mean velocity gain. Each point represents the average velocity gain ± S.E.M. of 6 subjects, in the range 1.0 - 2.0 Hz. ** P<0.01, paired t-test relative to "BE" value. Velocity gain was significantly lower each day immediately after TR, returning to normal in about 20 minutes. The decrease in gain caused by TR was smaller after 3 days.

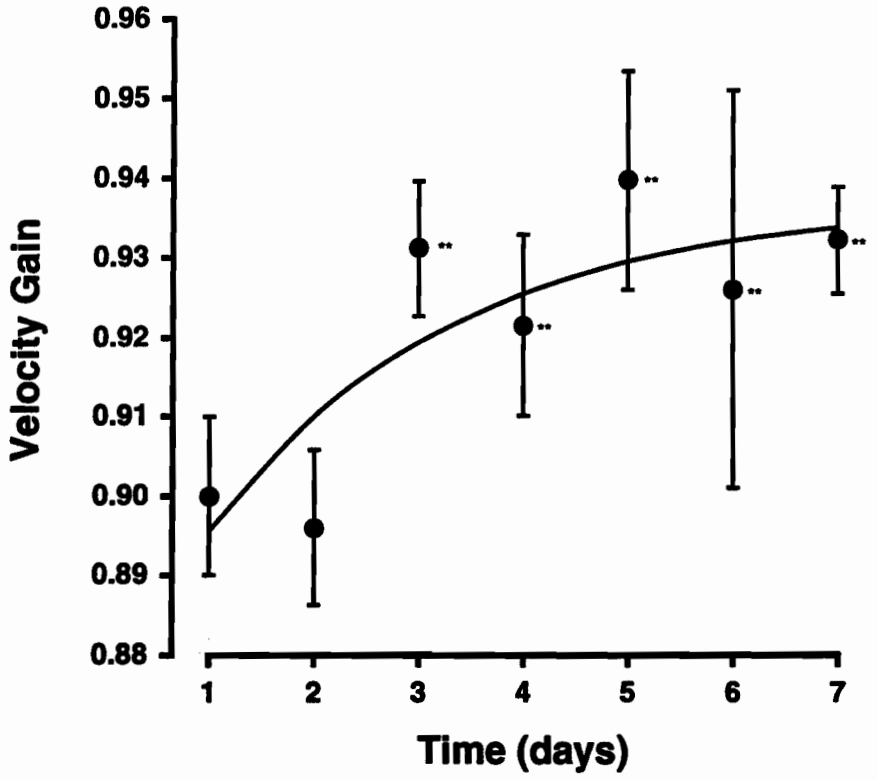

Figure 5.6 Long-term effect of TR on velocity gain. Comparison of the 7 "IA" points. The last 5 days were significantly higher than the first 2 (** $P<0.01$, paired t-test relative to the day 1 or day 2 point). The continuous line is an exponential fit to the 7 data points with a time constant of 2.3 days (least squares method, $R^2 = 0.694$).

DISCUSSION

VELOCITY GAIN ANALYSIS AS A METHOD TO EVALUATE GAZE CONTROL.

A series of technical problems forced us to adopt the present method for looking at gaze stability in humans. The results we obtained in the "BE" tests are measurements of gaze stability in normals, and therefore directly comparable to results published in the literature. Active head shaking tests in the light have been done in human subjects by other groups (5-9). In all cases, gain and phase in the 1.0 - 2.0 Hz range were compatible with our results: gain was essentially unity (0.9 - 1.1) and phase was negligible (+5° in 6 and -5° in 9).

GAZE INSTABILITY: OBJECTIVE EVALUATION VERSUS SUBJECTIVE PERCEPTION.

Interpreting subjective perception of gaze instability can be very difficult. The latter is a complex phenomenon that depends not only on the effectiveness of the gaze control system but also on the characteristics of the input. In this experiment, we obtained independent measures of head displacement and velocity gain. The former was seen to increase immediately after TR by an amount that was approximately the same on each of the seven testing days. In contrast, the latter was decreased immediately after TR but this change became smaller with each successive day. Thus all of the reported improvement in subjective gaze stability appears to have been a result of a long-term change in the gaze control system.

POTENTIAL NEUROPHYSIOLOGICAL SYSTEMS RESPONSIBLE FOR THE IMPROVEMENT IN GAZE STABILITY.

On the basis of the previous study (Chapter 4), we know that the improvement in gaze stability does not result from long-term changes in the VOR. Unfortunately, head shaking in the light does not allow one to discriminate between other neurophysiological systems that might have supplemented the suppressed VOR. At least three candidates could be suggested, however: vision, the cervico-ocular reflex (COR) and prediction.

Although the classical cut-off frequency for visual influences on ocular fixation during head movements is 1-2 Hz (6, 14), Demer et al. (15) have shown contributions of vision up to 4-6 Hz. Therefore, velocity gain could be enhanced by an increased contribution of vision.

The fact that gaze control can rely on more than just the VOR during normal head movements was well demonstrated by Dichgans et al. (16) in monkeys: one to two months after bilateral vestibulectomy, gaze stability partially recovered as the animals increased the gain of their cervico-ocular reflex (COR).

The role of the COR in normal human beings is negligible (17) but has been shown to be potentiated in bilateral vestibular patients (1, 2). The transient signs and symptoms caused by TR are in many ways analogous to those experienced after a vestibular lesion. If this comparison is appropriate, then one could argue that adaptation to both situations might involve the same mechanisms.

Prediction can be separated into 2 classes. Subjects could use a cognitive process to perform better *during the test only* by learning where the target should move to during head shaking (18). Alternatively, they could perform better *at all times* by utilizing an efferent copy of the motor signal to

the neck muscles to drive their eyes (19). Either mechanism could be used under the present circumstances, although the day-to-day improvement in gaze stability seemed to be present regardless of what the subject was doing.

GAZE STABILITY AND MOTION SICKNESS

The improvement in gaze stability reported here is correlated with the time course of adaptation to motion sickness, but this *does not* indicate a causal relationship. The facts that TR causes motion sickness even if the whole experiment is done in the dark (Chapter 3) and that blind people can get motion sick (20) and adapt to the malady (21), are clear evidence. However, while there is no causality, the correlated recovery suggests a common underlying adaptive mechanism.

The improvement in gaze stability without a concomitant improvement in VOR function implies a relative de-emphasis of the vestibular system as a reference source for oculomotor control, with other systems taking over. Perhaps at the same time, the neural mechanisms that produce motion sickness are less influenced by inappropriate vestibular signals, including those present for a short while after TR. This hypothesis of vestibular de-emphasis would lead to a "transferable" and "general" type of adaptation (to cars, buses, etc.), but not to absolute protection (such as after recovery from bilateral labyrinthectomy). Qualitatively, this has been the experience of subjects performing repeated TR in this and other experiments.

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Chapter 6

Effects of Acute Changes in Vestibular Function on the Control of Voluntary Head Movements.

INTRODUCTION

The control of head movements is a complex act involving such factors as voluntary drive, vestibulocollic and cervico-collic reflexes, vision, neck viscoelastic properties and head inertia. The exact contribution of each component is often unknown (1). During rapid perturbations, the vestibulocollic reflex (VCR) is used to automatically maintain head stability relative to inertial space (2, 3). Suppression of this system is therefore required during voluntary head movements. Even though pathways capable of modulating the VCR have been described in anesthetized animals (4-6), their mode of action in the fully awake, behaving subject remains to be defined (7).

"Torso Rotation" (TR) is an effective means of producing an acute, reversible change in human vestibular function through prolonged and excessive suppression of that system (8). Not surprisingly, a frequent consequence of the method is motion sickness. However, with repeated exposure, the signs and symptoms no longer appear. The primary goal of these experiments was to look for neurophysiological changes that might parallel this adaptive process (Chapters 4 and 5). This paper addresses a secondary but related issue: how do generalized changes in vestibular function (as reflected in the more specific vestibulo-ocular reflex) affect the control of voluntary head movements?

These results have been presented previously in the form of an abstract (9).

METHODS

TORSO ROTATION

A complete description of this method has been published elsewhere (10 and Chapter 3). In summary, subjects were trained to sweep their gaze back and forth between targets located 135° left and right of straight ahead. This paradigm required simultaneous motion of eyes (±135°), head (±90°) and torso (±45°) all in the same direction. Torso Rotation (TR) was performed continuously for 30 minutes at 0.7 Hz, following a sound cue.

CONTROLLED MOTOR ACTIVITY

Normal motor activity after TR also had to be standardized, to ensure that all subjects recovered in a reasonably controlled fashion. To achieve this goal, a simple task was designed, consisting of reorienting to a series of random numbers on the walls of a small cupboard. This task was performed continuously between the 3 post-TR tests. Further description of this method can be found elsewhere (Chapter 4).

MEASUREMENT OF VOR GAIN

The vestibulo-ocular response (VOR) gain was measured using a modification of Gauthier and Robinson's step rotation technique (11). These results have been reported in Chapter 4. In short, subjects were rotated in the dark 10, 20 or 30° to the left or right of straight ahead while keeping their eyes on their mental image (not afterimage) of a distant earth-fixed target. Net VOR gain was defined as the angle covered by the eyes during the rotation divided by the angle they should have covered, determined from eye position after the last refixation saccade in the light. Occasional saccades occurring during the rotation were extracted using an interactive computer

program that scanned the reconstructed gaze trace, looking for abrupt changes in eye position. The portion of the gain due to non-saccadic eye movements will be referred to as Smooth Phase VOR gain.

HEAD SHAKING TEST

In a separate experiment, a second set of subjects were instructed to shake their heads approximately 15° to either side of straight ahead while looking at a wall-fixed target 4 meters in front of them. These results have been reported in Chapter 5. The pace was set by a sound cue that swept from 3.0 Hz down to 0.3 Hz for 5 subjects. The sweep was reversed for the 6th participant, who shook his head from the lowest to the highest frequency. All subjects were specifically and carefully instructed to maintain the same head shaking amplitude at all times. Only data in the range 1.0 - 2.0 Hz were analyzed. The upper limit was the highest frequency attained by all subjects in all tests. The lower limit was set at 1.0 Hz, the frequency below which peak-to-peak head displacement became variable and inconsistent from day to day in any given subject. This increased variability was associated with a change in the way subjects moved their heads in that frequency range. The velocity profile turned to a square wave, i.e. they moved their heads at more or less constant velocity between beeps. The amplitude of the movement was therefore proportional to the velocity they had chosen and inversely proportional to the beep frequency.

Average peak-to-peak head displacement in the 1.0 to 2.0 Hz range was then calculated for each test. Subsequently, this value was normalized to the mean of days 2 to 7 "BE" sessions. (Day 1 "BE" was lower than all other points, resulting most likely from the subjects lacking familiarity with the experiment and therefore was not included in the calculation of the normalization factor (see Figure 6.3).

TESTING SCHEDULE

Each experiment lasted 7 days. On each day, measurements were obtained before ("BE"), immediately after ("IA"), 10 minutes ("10") and 20 minutes ("20") after Torso Rotation. None of the subjects had a known history of vestibular problems. All experiments had been approved a priori by a committee on human ethics.

RESULTS

MEASUREMENT OF VOR GAIN

Results of the 7-day VOR experiment, averaged across the 6 subjects, are shown in Figure 6.1. Mean VOR gain ± one standard error of the mean (S.E.M., n=6) has been plotted against time. The gain dropped significantly ($P<0.01$) each day immediately after Torso Rotation and returned to normal within approximately 20 minutes. No long-term trends in gain reduction or recovery rates were observed.

HEAD SHAKING TEST

The analysis of gaze stability during voluntary head shaking was complicated by an unexpected factor: despite instructions, subjects did not maintain a constant head displacement from one test to the next. On the contrary, displacement increased systematically each day immediately after Torso Rotation, returning to normal within about 20 minutes. Figure 6.2 shows two raw head shaking traces in the range 1.0 - 2.0 Hz. The amplitude of head movements was larger at all frequencies after TR. Normalized average amplitude over the range 1.0 - 2.0 Hz for the group of six subjects (± S.E.M.) was then calculated and plotted as a function of time in Figure 6.3.

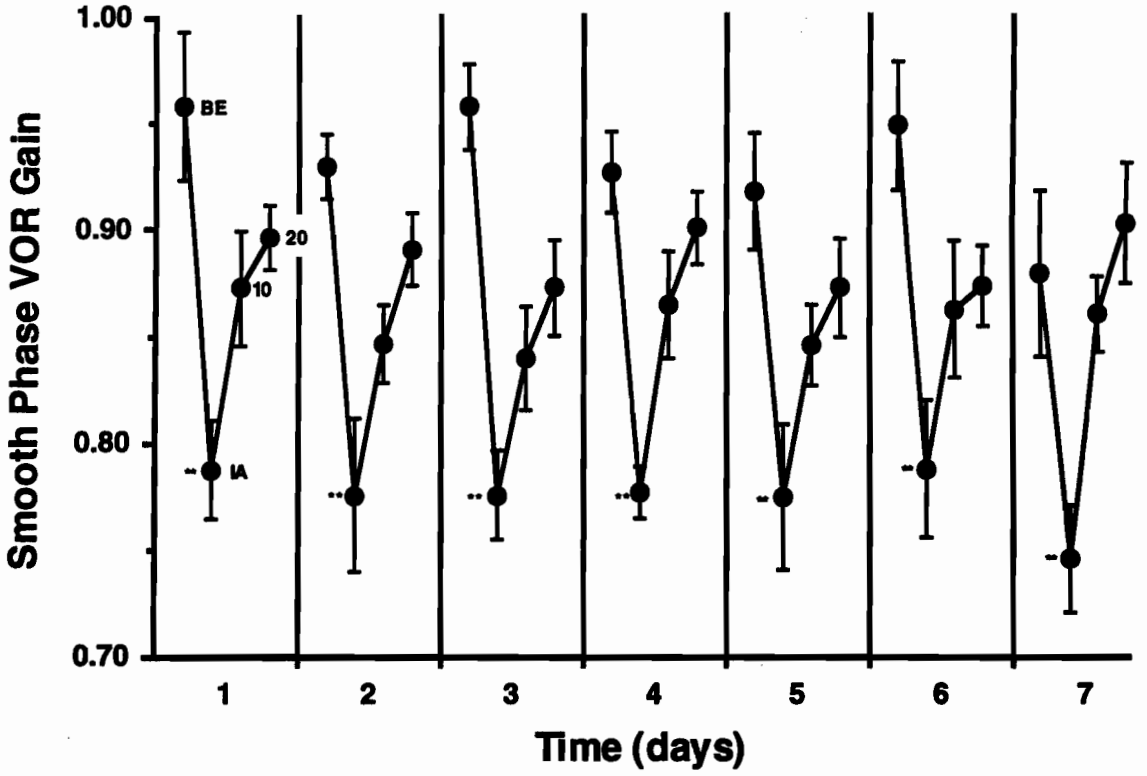

Figure 6.1 Effects of repeated exposure to TR on group mean VOR gain. Each point represents the mean ± S.E.M. of a total of 144 rotations, in 6 subjects. ** P<0.01, paired t-test relative to "BE" value. VOR gain was significantly lower each day immediately after TR, returning to normal in about 20 minutes. No long term trend was observed. (Note this Figure is identical to Figure 4.7).

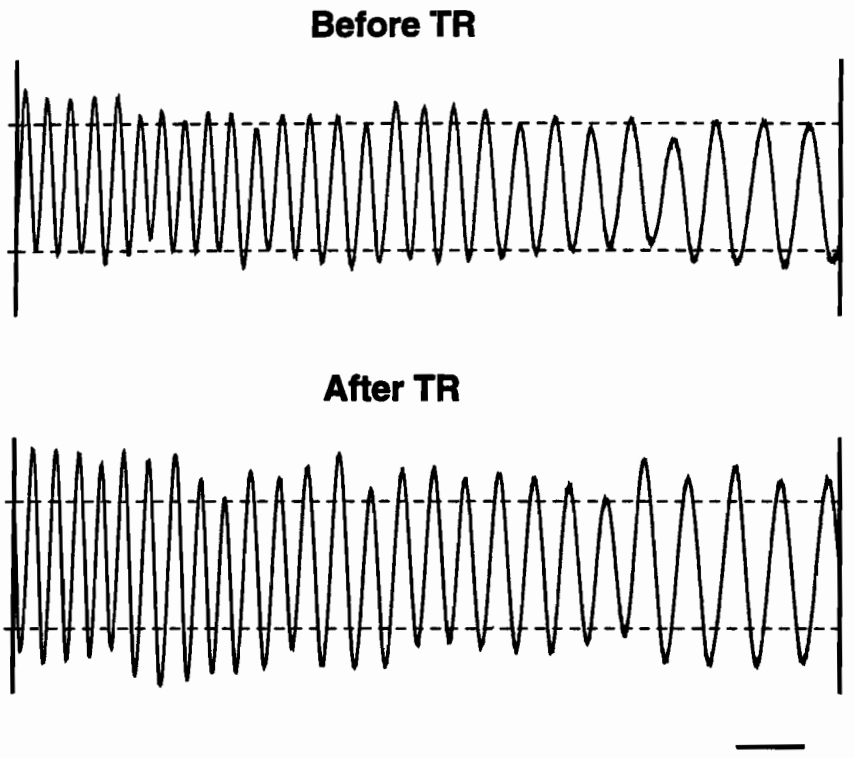

Figure 6.2 Comparison between 2 consecutive head shaking tests. Head displacement was larger at all frequencies immediately after TR compared to before TR. Dashed lines represent ±15°. Horizontal scale represents 1 second.

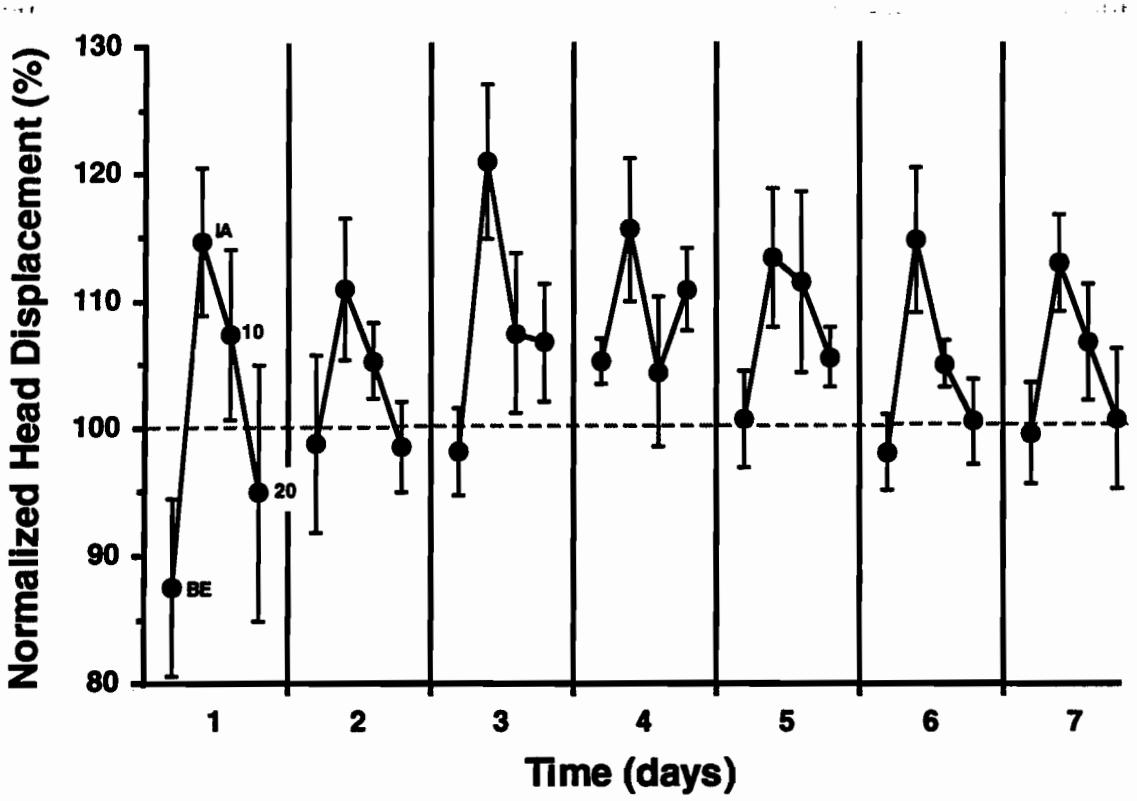

Figure 6.3 Effects of TR on mean normalized head displacement (±S.E.M.) of 6 subjects. A systematic pattern of changes in head displacement was seen each day after Torso Rotation. For each subject, data were normalized relative to the mean of the "BE" tests, excluding day 1 (see methods).

Except for the day 1 "BE" session, the daily changes were quite systematic, and no long-term changes were observed. The relatively smaller head displacement on day 1 "BE" was most likely due to a lack of experience.

CORRELATION BETWEEN VOR GAIN AND HEAD SHAKING AMPLITUDE

The overall pattern of change in head shaking amplitude seen in Figure 6.3 was inverted but otherwise strikingly similar to the change in VOR gain shown in Figure 6.1. To quantify this similarity, head displacement was plotted as a function of VOR gain (Figure 6.4). Since no trends were evident in either data set, the "BE", "IA", "10" and "20" results were averaged across all 7 days to produce the 4 points shown in this figure. When a first order least squares regression line was fit to these points, the correlation was remarkably tight ($R^2 = 0.996$).

DISCUSSION

POSSIBLE MECHANISMS BY WHICH TR COULD MODIFY HEAD MOVEMENT CONTROL.

Very little is known concerning the mechanism of action of TR, except that the nature of the movement suggests a great deal of vestibular suppression should be occuring and the result is qualitatively similar to a temporary vestibular lesion (Chapter 3).

There is also relatively limited knowledge of the neurophysiological processes underlying the control of *voluntary* head movements, so the possible site of action of TR at the single cell level is hard to infer. The close correlation between the change in head amplitude and altered vestibular function (evaluated using the VOR), as well as their parallel recovery, suggests involvement of the VCR, however. The role of this system is to keep

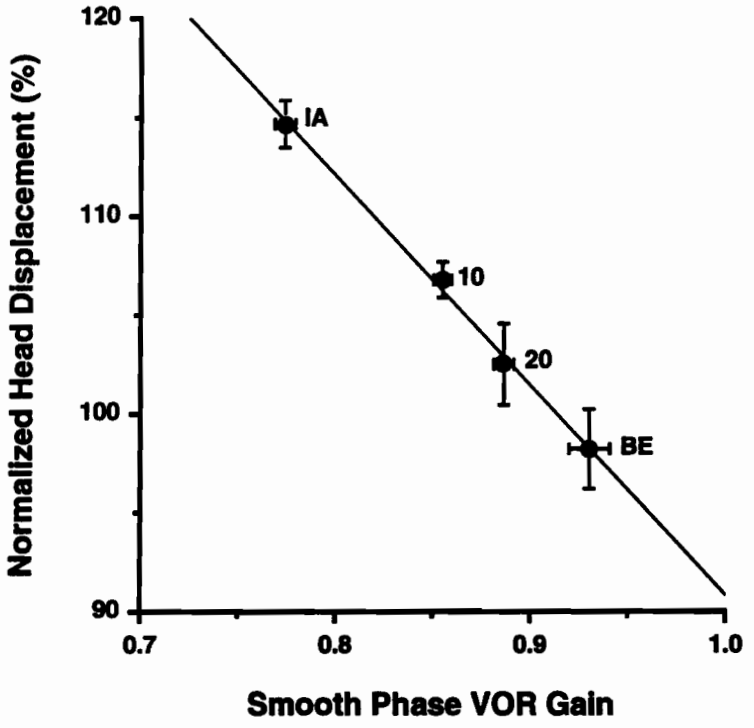

Figure 6.4 Head displacement - VOR gain correlation. Because there were no long-term trends in either data sets, the 7 "BE", "IA", "10" and "20" tests were averaged. Plotting the resulting head displacements against smooth phase VOR gain, we obtained this very tight correlation (least squares fit, $R^2 = 0.996$).

the head stable relative to inertial space (2, 3). It is also believed that in order to generate a voluntary head movement, the VCR has to be suppressed (e.g. 12). Electrophysiological experiments in anesthetized cats and rabbits have reported cells from the cerebellar vermis (4), interstitial nucleus of Cajal (5), and frontal eye field and neck motor cortex (6) that can modulate the VCR, providing further support to this theory. During TR, subjects probably suppress their VOR and VCR almost constantly. Perhaps the VCR remains suppressed for some minutes after TR, as is the case for the VOR (10). If that were true, then when a subject decides to make a voluntary head movement after TR, the central command sent to suppress the VCR might now be relatively too large, the net result being a head movement overshoot.

The story may not be this simple, however. Recordings made in *alert* cats have demonstrated at least two components to the VCR. The shorter-latency VCR was not suppressed during active head turns (7). In one of the four animals who had higher tonic EMG activity, the longer-latency VCR seemed to be modulated, however. These authors concluded that the VCR-modulating cells described above may therefore act via the indirect, longer-latency VCR, involving pathways such as the reticulospinal tract (reviewed in 13) rather than the more direct vestibulospinal tract (see 14).

Work done in humans suggests that the situation may be even more complex. Guitton *et al.* (15) have shown that up to 1 Hz, the latency of the response to maintain head stability is about 140 msec, way beyond reflex latencies. Furthermore, the gain of that response seems under voluntary control, as shown by a lack of head stability if the body is perturbed during mental arithmetic. The presence of a vestibular signal was necessary however, since vestibular patients could not perform the task at all. Above 1 Hz, such a slow response system would have a large phase lag and therefore

not be efficient. Based on a theoretical assessment, these authors estimated that head inertia became important only above 2-4 Hz. They therefore hypothesized that between 1 and 3 Hz vestibulo-collic responses should become more important if head stabilization is the current goal. This idea is supported by results from Keshner and Peterson (16), who used a similar paradigm but stimuli with components up to 4.55 Hz. In summary, the systematic changes observed in these experiments suggest that TR affects the voluntary head movement control system at a fundamental level, possibly involving the vestibulo-collic system. Further speculation on the site(s) where modifications occur will have to wait for further description of the neurophysiology of the normal system.

Other explanations are possible, however. One would involve the conscious perception of rotation. Subjects possess a distinct ability to estimate angle of rotation based on their memory of vestibular signals, as demonstrated using "Vestibular Memory-Contingent Saccades" (VMCS, see 17). However, the gain of VMCS is decreased after TR (8). If this implies decreased perception of rotation, and subjects are instructed to shake their heads back and forth using the same amplitude as before TR, then larger amplitude head movements could result.

Another mechanism that might be considered is the possible use of eye position as a reference during voluntary head shaking. If the cue to reverse the direction of head motion was a certain angle of the eye in the orbit, and VOR gain was abnormally low, head amplitude would have to increase. Furthermore, there would be a very tight relationship between head amplitude and VOR gain, as described here. This explanation is unlikely, however, since the overshoot was as pronounced at 1 Hz as it was at 2 Hz (Figure 6.2). At 1 Hz visual tracking kept the subject's gaze on the target, so

both head *and* eye amplitude were increased.

Finally, efferent pathways to the labyrinth have been described in different species (reviewed in 18). Although their functional significance is still debated (19, 20), one might speculate that TR in some way modifies the function of the peripheral organs through efferent control. However, if TR is followed by 20 minutes of controlled motor activity *with the eyes closed*, postural stability returns to normal within that period, but gaze stability does not improve. This suggests a more central basis for the effects of TR.

ALTERED HEAD MOVEMENT CONTROL FOLLOWING VESTIBULAR LESIONS.

Whatever the underlying mechanism, these observations show once again that vestibular feedback plays an important role in the control of voluntary head movements. It is well known that most patients attempt to compensate for a vestibular lesion by reducing those movements (21). However, there are many situations (including this experiment) in which the head *must* be moved, and in those cases overshooting would be expected to occur. Conversely, it would be difficult to keep the head stable in demanding situations such as locomotion (22).

Changes in eye-head coordination have been observed after "canal plugging". This procedure creates a very selective vestibular deficit by carefully drilling through individual semi-circular canals. Bone dust packed into the opening blocks the canal in question, without compromising the rest of the vestibule (23). The effects of bilateral horizontal canal plugging on combined eye-head gaze shifts have been studied in cats by Fakhri et al. (24). Results from this study are similar to ours: after surgery, the animals made large head overshoots when reorienting to a target. This occurred both in the dark and in the light (larger errors were seen in the dark). About 4 weeks

after surgery, the size of the overshoots stabilized, but remained present. Recently, canal plugging has been used as a surgical procedure to alleviate intractable benign paroxysmal positional vertigo in humans (25). These authors have not reported the effects of the surgery on head movement control, but difficulty controlling amplitude might be anticipated.

The strategy used to compensate for altered vestibular function can vary between species, driven partly by differences in oculomotor range (OMR). Cats have a small OMR, and therefore are forced to rotate their heads a great deal both during testing and normal activity, effectively making any change in head movement control easily identifiable. Primates and humans on the other hand have much larger OMRs and can therefore choose a variety of motor strategies during adaptation (see 26 Fig. 9), potentially hiding any effect of the vestibular loss on head movement control. Recovery of eye-head coordination after bilateral labyrinthectomy in monkeys involves at least 3 mechanisms: increased gain of the cervico-ocular reflex (COR), emergence of preprogrammed compensatory eye movements, and recalibration of the saccadic system (26). In humans, Kasai and Zee (27) and Watt and Peterson (28) showed that different patients seem to adopt different strategies. However, recovery seems to involve a moderate increase in the gain of the COR (27, 29), a reflex that has such a low gain in normals that it is not believed to contribute to gaze stabilization (30).

GAZE INSTABILITY FOLLOWING VESTIBULAR LESIONS.

Vestibular patients often report that their visual scene appears unstable when they move their heads too fast. Presumably, they have abnormally low VOR gains, resulting in gaze slip proportional to the velocity of head movement. If their reduced vestibular function also leads to larger amplitude and hence higher velocity head rotations, this would cause even

greater gaze slip, at least until they learn to deliberately slow their heads. Thus, a relatively minor change in vestibular function can be amplified by simultaneously compromising two independent output pathways.

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The Role of Vision in the Long-term Improvement in Gaze Stability.

INTRODUCTION

"Torso Rotation" (TR) is an unusual motor strategy that acutely modifies vestibular function. The short-term changes following a single, short (30 minutes) exposure include perceptual illusions during movement, gaze and postural instability, a significant decrease in vestibulo-ocular response (VOR) gain and the appearance of motion sickness signs and symptoms (1 and Chapter 3).

With repeated daily exposures, longer-term changes have been demonstrated: motion sickness susceptibility disappears (Chapter 4) and post-TR gaze instability is reduced (Chapter 5), with similar time constants (about 2 days). Nevertheless, VOR gain is suppressed identically by repeated TR sessions (Chapter 4). These findings led us to suggest that the long-term compensatory mechanism probably involved a relative de-emphasis of the vestibular system as a reference source (Chapter 5): following repeated exposure to compromised vestibular signals (such as after TR), the brain would learn to rely less on vestibular inputs, and give more weight to one or more alternative sensory signals. These could include vision (2), the cervico-ocular reflex (3-5), predictive mechanisms (reviewed in 6), and efference copy (7).

This experiment is the first of a series of two (with following Chapter), designed to identify the neurophysiological system(s) responsible for the long-term improvement in overall gaze stability measured after TR. The role of vision will be assessed by comparing results obtained during head shaking in the dark (presented here) to those of head shaking in the light (Chapter 5).

These results have appeared previously in abstract form (8).

METHODS

Six subjects (3 male, 3 female; age range 24-50) with no prior history of inner ear problems participated in this experiment, following its approval by the Research Ethics Board, Faculty of Medicine, McGill University.

TORSO ROTATION

TR is a form of self-generated, rhythmical movement. Following a 0.7 Hz sound cue, subjects were required to sweep their gaze back and forth between 2 targets located 135° on either side of straight ahead, continuously for 30 minutes. Combined movements of the eyes, head and torso were necessary to see the targets. Further descriptions of the technique have been published elsewhere (1 and Chapter 3).

CONTROLLED MOTOR ACTIVITY

To standardize the rate of recovery from a 30 minute exposure to TR, subjects performed a series of stereotyped movements between tests. The procedure used here was slightly modified from the number retrieval task that we had used previously (Chapter 4), to allow a tighter regulation of the movement pace. The subject was surrounded by four 2 meter high poles (90° apart), each of which had 3 small red LED targets (at, 51 cm above and 76 cm below eye level). Following a rapidly-paced cue tape (pseudo-random sequence, new command every 2-2.5 sec), the subject had to reorient his whole body to the new direction given by the tape (left, right or behind), pointing his nose at the appropriate target (up, center or down).

RED LIGHT

To minimize any effect of repetitive light/dark transitions on EOG gain (9), subjects were maintained in low intensity red light from 30 minutes prior to the beginning of the experiment until the end of data collection, 24 minutes post-TR. Other precautions were also taken, such as using small red LEDs as targets for the controlled motor activity, in order not to alter the corneo-retinal potential.

RECORDING EQUIPMENT

Data for this experiment were acquired using a custom-made, self-contained digital data acquisition system, consisting of two units (Figure 7.1). The one worn on the head contained a 3-axis angular rate sensor (Watson Industries, ±1000°/sec), an EOG pre-amplifier and a thermistor (for rate sensor calibration). It measured 7.4 x 7.4 x 12.4 cm and weighed 0.55 kg. It was connected by a light weight, flexible cable to a larger unit located on the subject's back, measuring 6.6 x 14.5 x 26.4 cm and weighing 1.7 Kg. This unit contained another 3-axis rate sensor (±300°/sec), a thermistor, the complementary EOG amplifier circuitry, filters (DC-200 Hz 8 pole Bessel for EOG, DC-50 Hz 2 pole Bessel for head yaw and DC-25 Hz 2 pole Bessel for the others), a 12 bit A/D converter, a custom-made microcomputer (based on a Motorola 68000 chip) and an insertable 5 megabyte flash memory module (White Technologies). To prevent aliasing, sampling rates were adjusted to be at least twice the filter's cut-off frequency for individual channels (512 samples/sec for EOG, 128 samples/sec for head yaw and 64 samples/sec for the others). With these settings, one flash memory module could provide up to approximately 45 minutes of continuous recording. Because the mass of the head unit was located near the axis of rotation during head yaw movements,

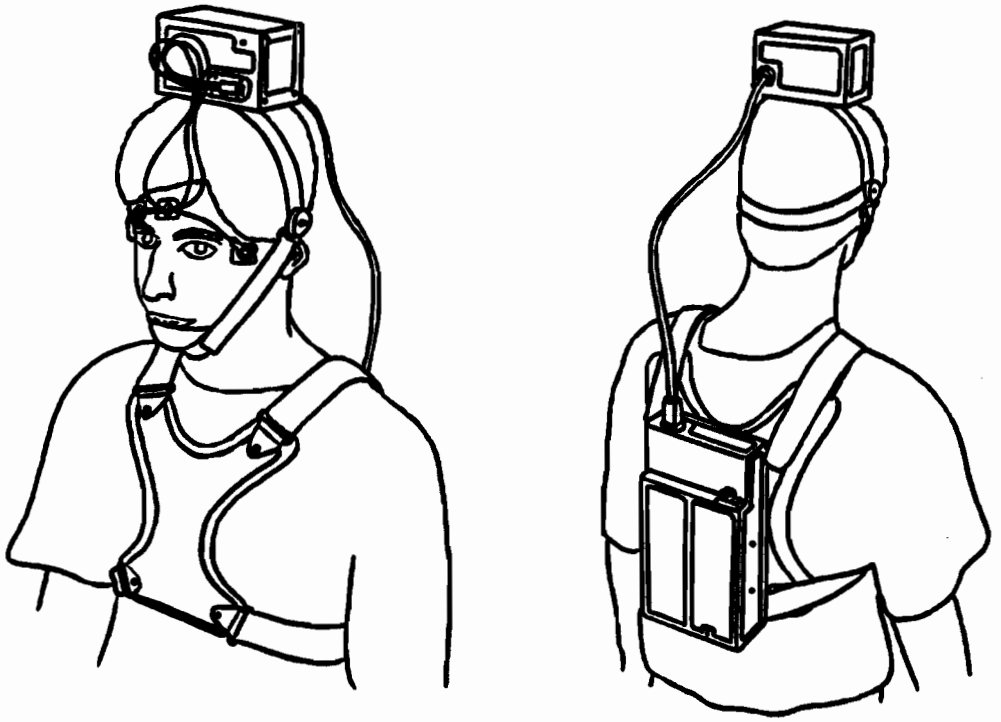

Figure 7.1 Data were acquired using a novel, completely portable digital data acquisition system. The head unit contained a 3-axis angular rate sensor and EOG pre-amplifier. The torso unit contained another 3-axis rate sensor, the EOG amplifier, Bessel filters, a 12 bit A/D converter, a 68000-based microcomputer, 5 MB flash memory and batteries. In its present configuration, this set-up can provide up to 45 minutes of continuous recording.

slippage of the head unit was very small (max torque applied to unit calculated to be 0.0471 N•m at 2 Hz, ± 15°), so head movements could be measured quite accurately.

HEAD SHAKING TEST

Gaze stability without visual inputs was evaluated during active head shaking in the dark. Subjects were instructed carefully to shake their heads at a fixed amplitude (about ±15°) while trying to maintain their gaze on an imagined, distant earth-fixed target. They also had to constantly change the frequency of their head movements, sweeping from 3.0 Hz down to 0.3 Hz, guided by an auditory cue.

To prevent any falls, particularly after TR, subjects performed the tests while standing inside a large, open-topped steel drum bolted to the floor. The diameter of the drum (58 cm) was adequate to provide no tactile cues as long as the subject remained upright. In the case of a sudden loss of balance, the height (84 cm) and strength of the barrel were appropriate to catch the subject. In addition, infrared video monitoring was provided to the experimenter who could turn on the red light and enter the room at any time during the test. In practice, subjects only rarely lost their balance.

EOG CALIBRATION

As in all TR adaptation experiments (Chapters 4, 5, 7, 8), testing had to be done in a very short amount of time, due to the rapid return to normal of at least some of the neurophysiological changes caused by the technique. In order to obtain a rapid, full range EOG calibration, subjects were instructed to stare at a distant, earth-fixed target (in red light) and to rotate their heads in small steps (about 7°) up to a maximal lateral excursion of about 30° to

either side of straight ahead. Pauses of about 0.5 seconds between successive steps were requested to allow acquisition of sufficient steady-state data.

TEST SCHEDULE

The test schedule designed for the previous TR adaptation experiments (see Chapter 4) was also used here. In summary, on each of 7 consecutive days, there were 4 test sessions: before TR ("BE"); immediately after TR ("IA"); 10 minutes after TR ("10"); and 20 minutes after TR ("20"). During each of these sessions, 2 tests were performed in quick succession: "head and torso" shaking followed by "head-only" shaking, both in the dark (Figure 7.2). "Head-only" shaking is the topic of this Chapter. "Head and torso" shaking will be discussed next (Chapter 8). EOG calibrations were obtained before, between and after these tests. Controlled motor activity was performed between the "IA" and "10", and "10" and "20" sessions.

FILTERING

Following each experiment, data were transferred to an Everex 386 computer for analysis. All signals, after digital low pass filtering (F_c=10 Hz, Hamming window (10) with a number of points proportional to their sampling frequency), were undersampled at 64 samples/sec (highest common sampling frequency) and synchronized using linear interpolations.

VELOCITY GAIN ANALYSIS

The method presented for the analysis of head shaking in the light (Chapter 5) was also used here. Briefly, "velocity gain analysis" consisted of pooling consecutive cycles of head movement according to their frequency, in bins 0.2 Hz wide, in the range 0.3 - 4.0 Hz.

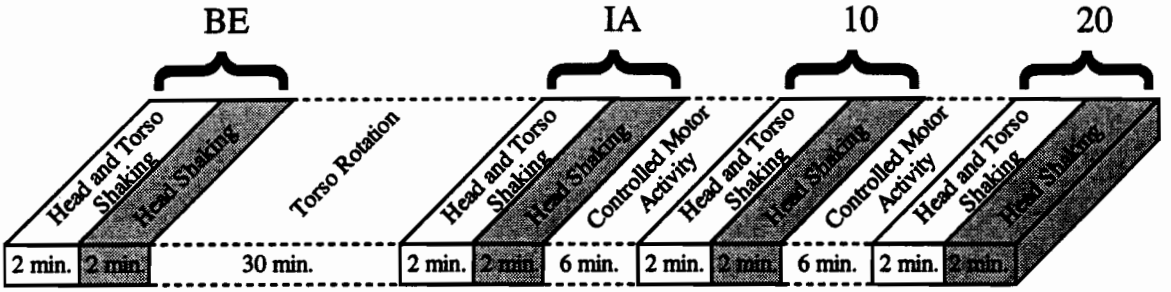

Figure 7.2 Data presented in this and the following Chapter were acquired in quick succession. The sequence presented above was repeated on 7 consecutive days. "Head and torso" shaking, as well as "head-only" shaking were carried out in total darkness. The rest of the time was spent in low intensity red light.

For each bin containing more than 1 cycle of data, a graph of instantaneous eye versus instantaneous head velocity was constructed after interactive removal of saccades and compensating for phase (see below). A first order least squares fit was then calculated for all the points on the graph. The slope of the fit represented the velocity gain for the frequency range covered by that graph.

PHASE ANALYSIS

Phase evaluation was conducted by changing the synchronization between the eye and head velocity signals while looking at the velocity gain plots described above (see Figure 7.3). On command, the eye trace could be moved left (phase lead, negative value) or right (phase lag, positive value) with respect to the head trace, in increments of 1 data sample. Phase was determined when the minimal amount of scatter on the plot was reached. The smallest phase difference that could be discriminated by this technique was therefore limited by intersample interval, in this case 15.6 msec (1/64 Hz). Noise was very low due to signal filtering (see above), and for most subjects only interfered with phase measurements for frequency bins under 0.6 Hz.

GAZE STABILITY DURING EOG CALIBRATION

This analysis was added *after* the completion of the experiment, to confirm reports made by all six participants that (i) performing the EOG calibration was unusually difficult immediately after TR due to image slip during movement and (ii) after 1-2 days, gaze instability during post-TR calibrations was reduced.

As the frequency content and peak velocity of eye and head movements during EOG calibrations were lower than during head shaking, the corner frequency of the digital filters was reduced to 4 Hz. The calibration was then

divided into a series of consecutive movements. A 1 sec window (64 samples), centered at peak head velocity, was defined for each movement. All movements containing blinks or performed in the non-linear portion of the EOG range (beyond about ± 35-40°) were rejected. For each subject-session (i.e., "BE" or "IA"), mean eye and head velocity profiles were calculated by averaging the non-rejected movements. To further simplify this evaluation of gaze instability, we confined the analysis to the first half of the head movement, where head velocity was increasing up to its peak. To allow inter-subject comparisons, head velocity bins 5°/s wide were defined in the range 0 - 50°/s. Mean eye velocity was calculated from all the points in any given bin. Finally, for each subject-session a plot of "mean" eye velocity versus head "bin" velocity was constructed (e.g. Figure 7.9).

RESULTS

RAW DATA

Figure 7.3 is an example of data after calibration, digital filtering and synchronization (see methods). The pattern of head velocity varied from almost sinusoidal at the higher frequencies to a wave form more closely resembling a square wave at the lower ones. Few saccades were seen, and tended to be concentrated at the lower frequencies. The amplitude of head shaking tended to be smaller in the dark than in the light, and decreased with increasing frequency.

VELOCITY GAIN

Figure 7.4 illustrates the velocity gain analysis method. Instantaneous eye velocity has been plotted against instantaneous head velocity for a frequency bin covering the range 1.6 to 1.8 Hz, after the effects of a minor

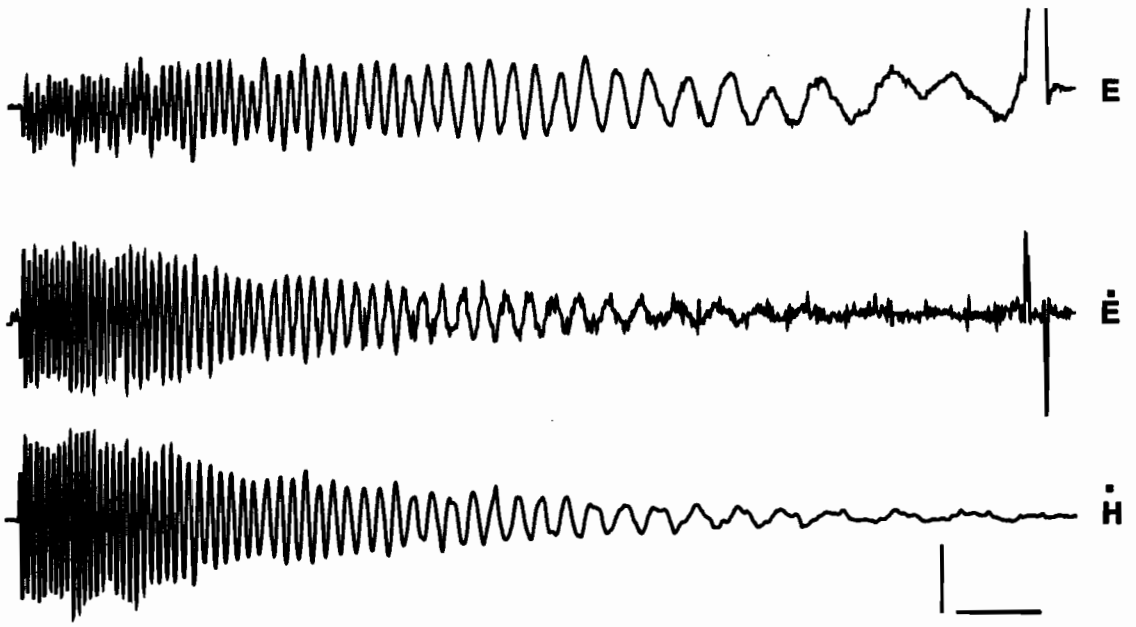

Figure 7.3 A complete head shaking session before "Torso Rotation". Signals have been digitally filtered, undersampled at 64 samples/sec and synchronized. Illustrated are eye position (E), eye velocity ($\dot{E}$) and head velocity ($\dot{H}$). The vertical scale represents 20° for the position trace and 200°/sec for the velocity traces. The horizontal scale represents 4 seconds.

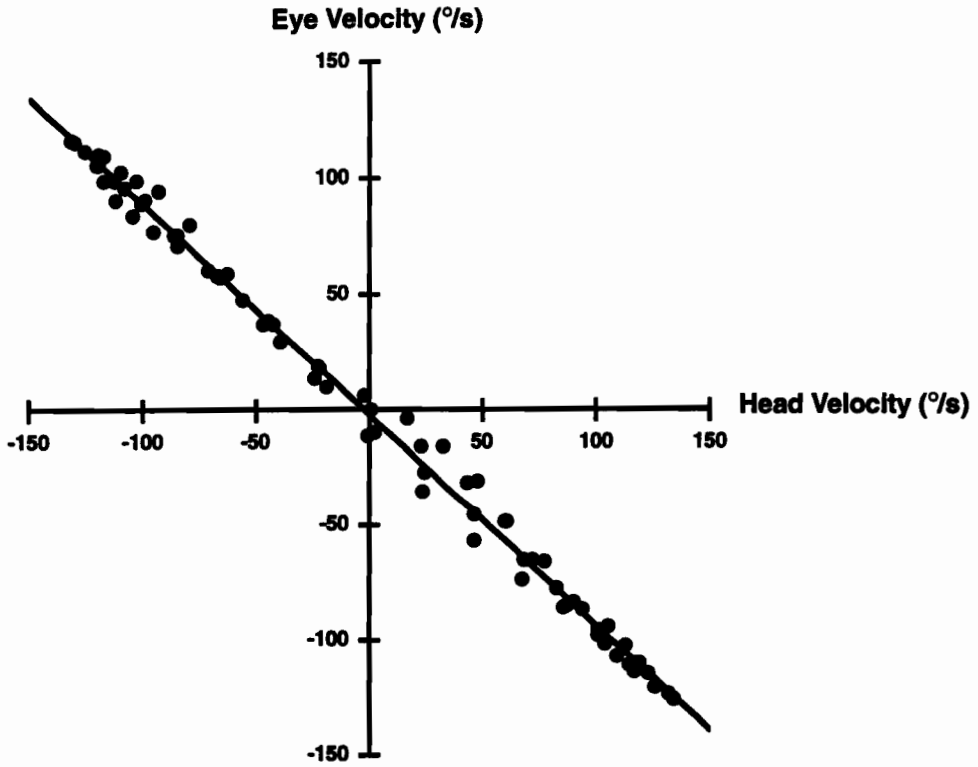

Figure 7.4 For each frequency bin (in this case 1.6-1.8 Hz), instantaneous eye velocity was plotted against instantaneous head velocity. The slope of the linear fit (least squares method) defines the term "velocity gain". In this particular example, velocity gain is -0.91 (R^2 = 0.995). Phase, removed before the fit, was +9.6°.

phase shift had been removed (see below). These data were taken from subject A, during the first day "BE" session, the same one that was presented in the previous figure.

PHASE

The smallest phase difference that could be resolved was dictated by the time interval between 2 consecutive data points and the frequency of head shaking (see methods). The sampling interval was 15.6 msec. As an example, this means that for a frequency bin centered at 1.7 Hz, such as in Figure 7.4, we can only resolve phase shifts in increments of 9.6° (360°/cycle * 1.7 cycle/s ÷ 64 samples/s). Even if our data were filtered and synchronized with extreme care, we have to consider a potential error of ± 1 sample interval during processing. In almost every subject-session in the entire experiment, however, phase was within ± 1 sample, and most often zero. We therefore consider phase to be 0°, within the time resolution limits of our analytical method.

FREQUENCY RESPONSE PLOTS

Once velocity gain was evaluated for all frequency bins in all 168 subject-sessions (4 per day * 7 days * 6 subjects), frequency response plots were constructed. Data from subject C day 2 are shown in Figure 7.5. Before TR (BE), velocity gain in the dark was close to unity at all frequencies (mean = 0.99). Immediately after TR (IA), velocity gain was decreased by about the same amount *at all frequencies* (mean = 0.73). While a certain amount of recovery was seen in the following 20 minutes in this case, on average that improvement was not statistically significant (see Figure 7.11, filled circles).

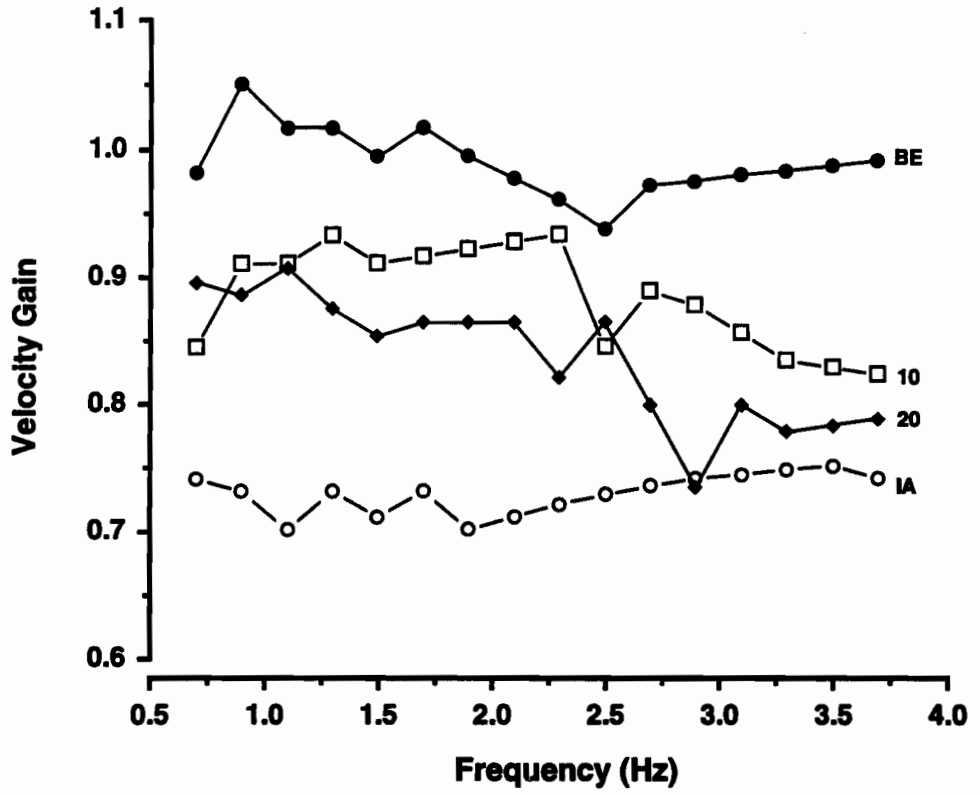

Figure 7.5 Frequency response curves for the four daily test sessions in one subject. Before TR ("BE"), velocity gain is close to unity at all frequencies, i.e. image slip is minimal. Immediately after TR ("IA"), the gain is reduced equally accross all frequencies tested. Phase, not shown, was almost always less than our time resolution limit. Gaze stability was not back to normal 20 minutes after TR ("20").

GROUP SUMMARY

Figure 7.6 summarizes the results obtained in our 6 subjects over 7 days. Data have been averaged in the 1.0 - 2.0 Hz range, in order to be comparable with those obtained during head shaking in the light (Chapter 5). Each day immediately after TR, gaze stability in the dark was reduced significantly (* $P<0.05$, paired t-test) by essentially the same amount. Note again the very small amount of recovery observed in the 20 minutes following TR.

COMPARISON TO VOLUNTARY HEAD SHAKING IN THE LIGHT

Three of the six subjects for this experiment had also taken part in the previous study of head shaking in the light (Chapter 5). Figure 7.7 represents the mean day 2 responses of these subjects. Before TR, velocity gain in the dark (BE/Dark) was somewhat lower than in the light (BE/Light) but the overall shape of both curves was similar. After TR, velocity gain in the dark (IA/Dark) was still lower than in the light (IA/Light) but the curves were not so similar due to a presumed contribution of visual tracking at the lower frequencies in the light.

THE ROLE OF VISION

In order to assess the role of vision in the *long-term* improvement in overall gaze stability, mean velocity gain for all 6 subjects determined immediately after TR has been plotted for each of the 7 days of testing in Figure 7.8. Head shaking in the dark is a much more demanding task, leading to substantially increased variability of the results. Nevertheless, the systematic and significant (** $P<0.01$) improvement in gaze stability observed after 3 days in the light (Chapter 5) was not present in the dark. The slope of

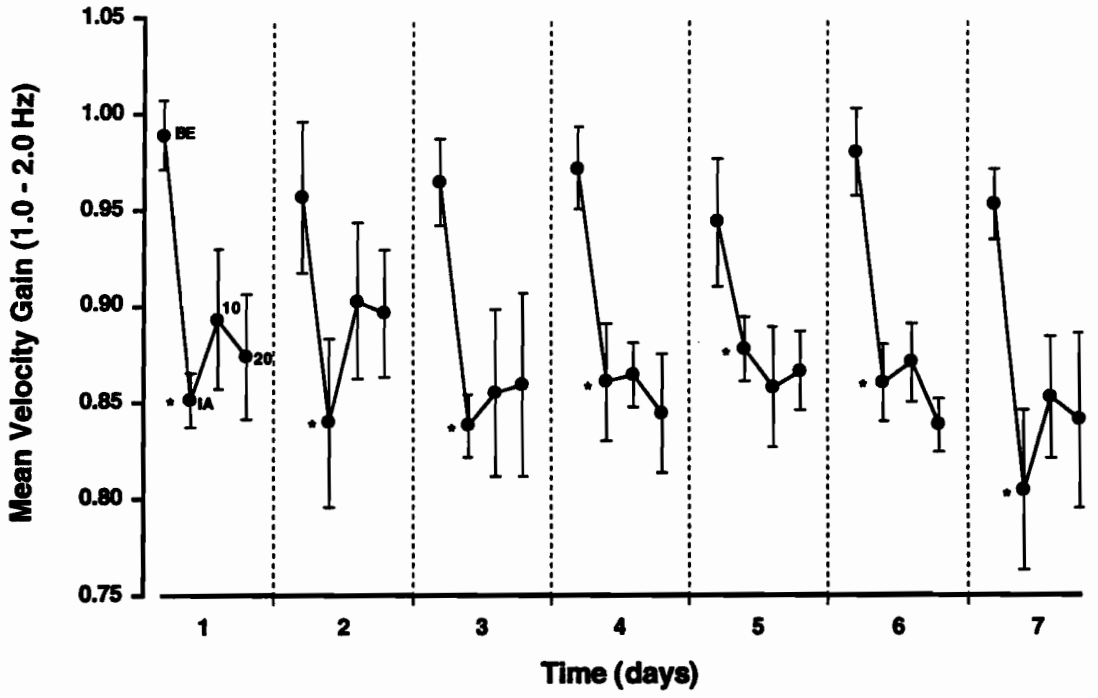

Figure 7.6 Effects of repeated exposure to TR on group mean velocity gain in the dark. Each point represents the average velocity gain ± 1 standard error for 6 subjects, in the range 1.0 - 2.0 Hz. Velocity gain was decreased by similar amounts each day immediately after TR (* $P<0.05$, paired t-test). Gaze stability did not return to normal in the 20 minutes following Torso Rotation.

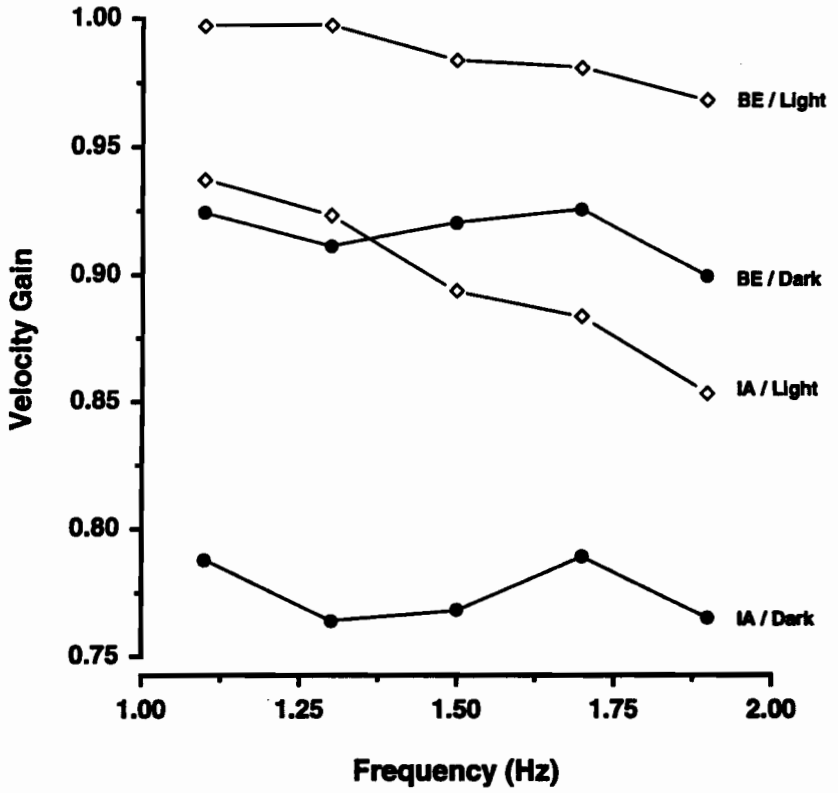

Figure 7.7 Comparison between head shaking in the light (diamonds) and in the dark (circles). Each point is taken from the average of the 3 subjects who participated in both experiments. After TR, visual tracking increases gaze stability at lower frequencies in the light.

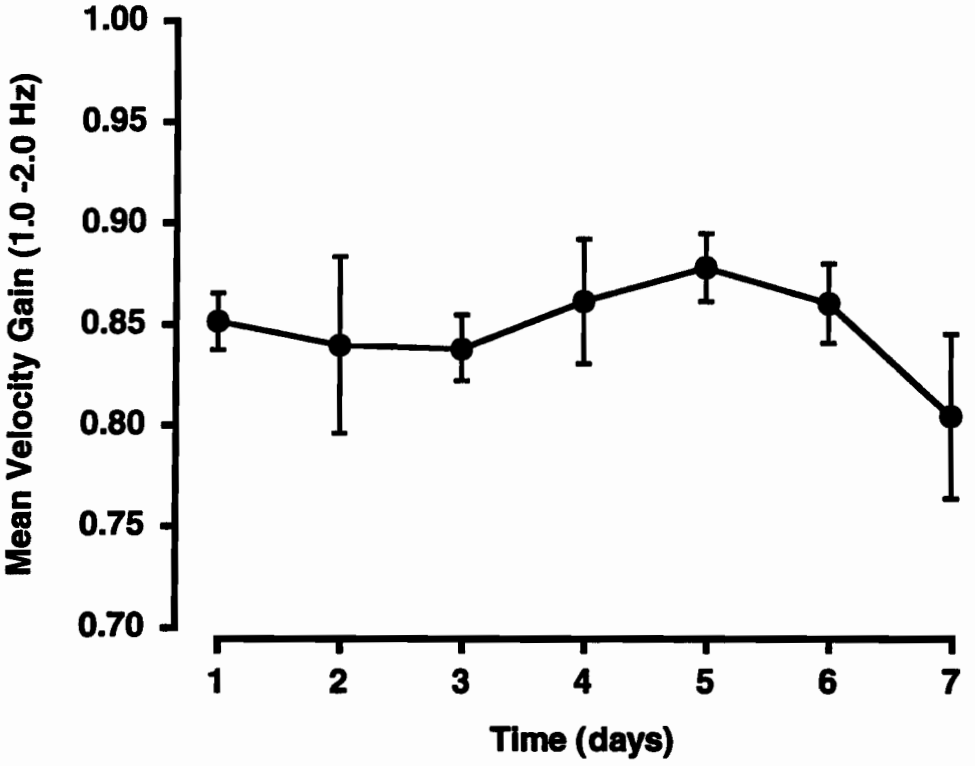

Figure 7.8 Mean velocity gain immediately after TR ("IA") for 6 subjects plotted for each of the 7 days of testing. The slope of a linear regression fitted to these data was not statistically significantly different from zero (P>0.9).

a linear regression line fitted to these data was not statistically different from zero (P>0.9). This lack of improvement was also clear during the independent "head and torso" shaking part of this experiment (Chapter 8).

GAZE STABILITY DURING EOG CALIBRATION

This analysis was not part of the original experimental plan and is therefore somewhat limited. Nevertheless, subjects were so convinced of their difficulty keeping eyes on target for the first few days that it seemed warranted. Unfortunately, 2 subjects (E and F) had to be rejected from the analysis because of poor performance during EOG calibrations on the first 2 days of the experiment, despite 1 or 2 3-hour training session(s) prior to the beginning of data collection. The EOG calibrations they produced on these two days were still quite adequate for their original purpose, however.

Eye versus head velocity plots for the 4 remaining subjects are shown in Figure 7.9. On the left hand side, the daily pre-TR (BE) sessions are presented. Thicker lines highlight the day 1 curves. Note the day-to-day similarity in peak head velocity for any given subject but the large differences between subjects. On the right hand side, the seven immediate after (IA) sessions are shown. Unlike before TR, subjects A, B and C appear to reach a point where eye velocity saturates on day 1. Subject D, however, never moved her head fast enough.

Figure 7.10 plots data from subject A day 1 (○) and day 2 (●) immediately after TR as a representative example of the change in saturation velocity exhibited by subjects A, B and C. Second order linear fits (R=0.999 for day 1 and 0.997 for day 2) have been used to extrapolate the day 1 results and show the substantial difference in gaze stability at head velocities beyond 25°/s.

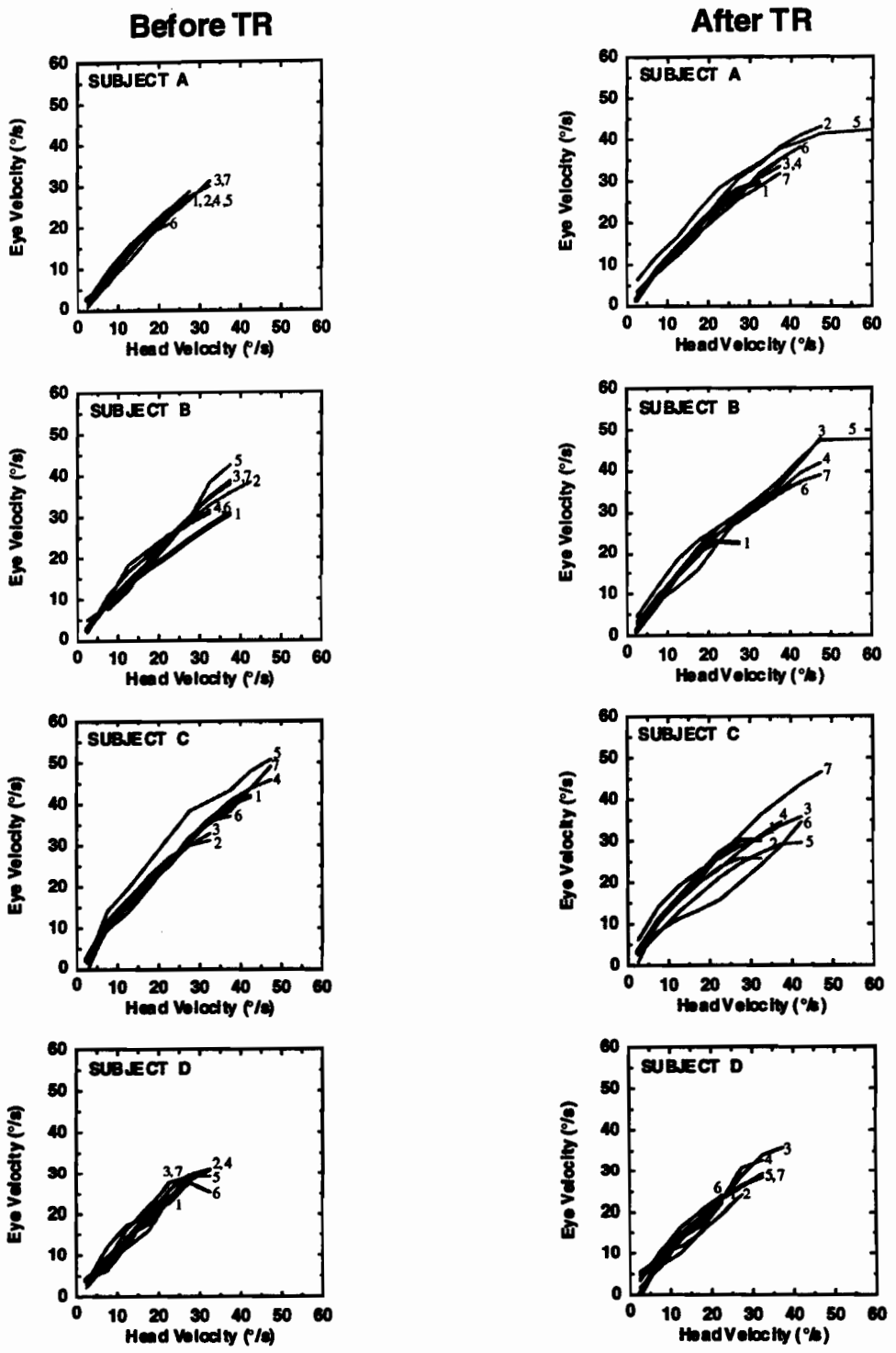

Figure 7.9 Gaze stability during EOG calibrations in red light. Each trace represents eye versus head velocity during the first half of the head movement. Each day is represented separately, and identified by a number from 1 to 7. Calibrations performed before TR are shown on the left, and immediately after, on the right. Day 1 results are emphasized by a thick dark line.

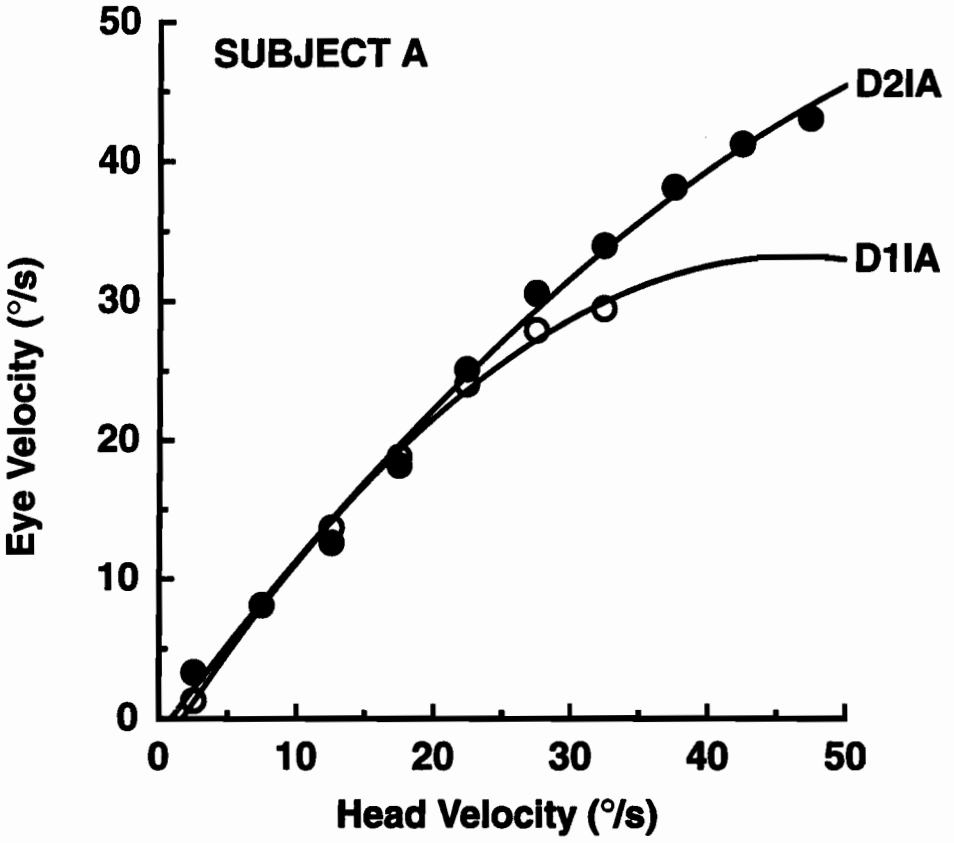

Figure 7.10 Example of the long-term improvement in gaze stability during post-TR EOG calibrations in red light. Day 1 (○) and day 2 (●) "IA" results from subject A. Line fits are second order linear regressions (R=0.999 for day 1, R=0.997 for day 2).

DISCUSSION

COMPARISON TO OTHER ACTIVE HEAD SHAKING TESTS

Velocity gain values obtained in the dark from our 6 subjects each day before TR were similar to, albeit somewhat higher than, those reported by others under analogous conditions (2, 11-13). When reported, phase was essentially 0°, also compatible with our findings.

The smaller "BE"-"IA" gain difference seen in Figure 5.5 when compared to Figure 7.6 can be explained by the stabilizing influence of visual tracking, especially at lower frequencies, in the former case (see Figure 7.7).

GAZE STABILITY DURING EOG CALIBRATION

Strategies used during EOG calibrations were variable from one subject to the next. Nevertheless, analysis of gaze stability during these movements confirmed subjective reports of day to day improvement. In addition, these data demonstrated that the improvement was not the second order effect of an inadvertent progressive lowering of head velocity from one day to the next, a strategy often used by vestibular patients (e.g. 14). In fact, it seems that if anything, the opposite was true. On the first day or two, peak head velocity IA was dictated by eye velocity saturation in three of the four subjects who could be analyzed. The fourth subject used head velocities that were small enough so that she never experienced gaze slip sufficiently large for our analytical method to pick up a saturation in eye velocity. This demonstrates that participants actively tried to maintain target fixation. If image slip became significant during the calibration, the only way to reduce it immediately was by making slower head movements. Later on, improved tracking ability allowed them to make what they would consider more normal head movements, and in 2 out of 3 cases *larger* head velocities were used

compared to "BE". The latter phenomenon has been described previously (Chapter 6).

THE LONG-TERM ROLE OF VISION

Despite the results reported previously for head shaking *in the light* (Chapter 5) and the data discussed in the preceeding paragraph, there was *no* long-term improvement in post-TR gaze stability over the 7 days of testing when head shaking was performed *in the dark* (Figure 7.8). These findings indicate that increased use of direct visual inputs must play a key role in the day to day improvement in gaze stability immediately after TR.

THE SHORT-TERM ROLE OF VISION

The present results also differ from those reported previously in that there was little recovery of gaze stability in the 20 minutes following TR each day, despite 2 periods of controlled motor activity (Figure 7.6). This finding is summarized in Figure 7.11, in which each point is the overall average for 6 subjects tested on 7 consecutive days. To show the relative degree of recovery, the data have been normalized relative to the difference between BE and IA. The open squares indicate gaze stability while shaking the head in the light (Chapter 5), the open circles show VOR gain measured using a step rotation method (Chapter 4) and the filled circles are the data from the present experiment.

The only difference between the 2 open symbol experiments and head shaking in the dark (other than the testing method) was room illumination. Since we used electrooculography to measure eye movements in the dark, it was necessary to dark adapt our subjects using low intensity red light prior to testing in order to have meaningful EOG gain calibrations (9). Dark adaptation takes a substantial amount of time, and it was not practical to

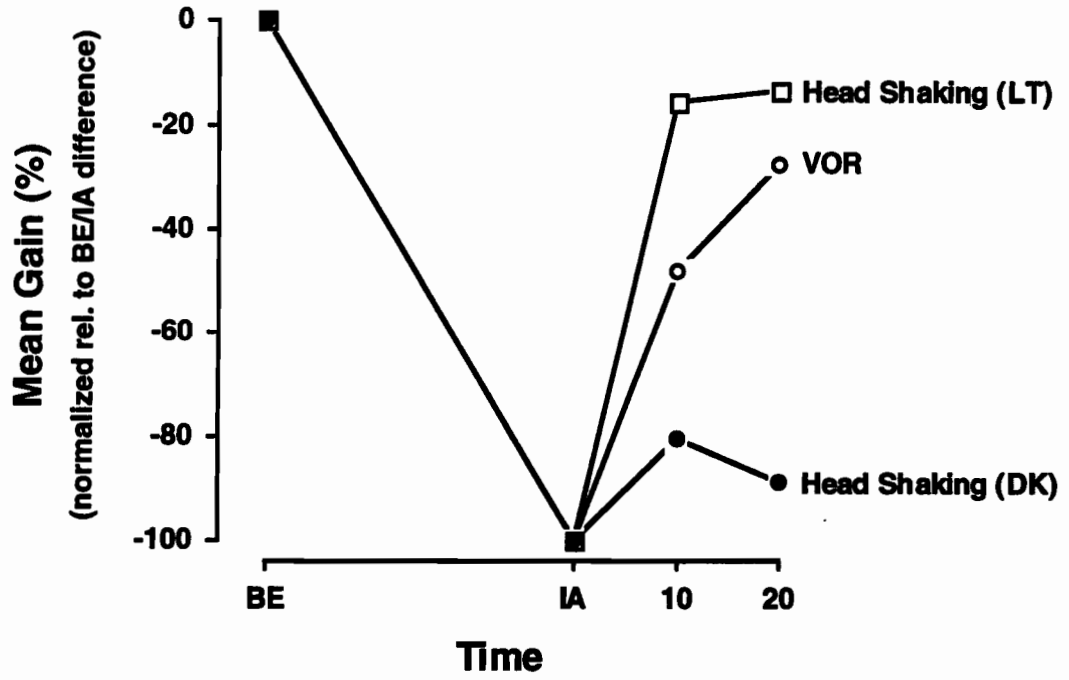

Figure 7.11 Comparison between head shaking in the light (□, Chapter 5), head shaking in the dark (●) and VOR (○, Chapter 4). Each point is the mean of data acquired on 7 consecutive days, in 6 subjects. Gain values have been normalized and expressed as a percentage of their respective "BE"-"IA" difference.

return to normal room light for TR or controlled motor activity (Figure 7.2). Apparently, visual inputs received in low intensity red light were *not* adequate to drive this short-term adaptive process.

LONG-TERM VERSUS SHORT-TERM MECHANISMS

The differences between the long and short-term roles of vision suggest that at least two independent mechanisms may be at work. The long-term (day to day) improvement seems to be a type of 'visual enhancement', as it requires *direct* visual feedback to operate and prolonged exposure to become effective. Once complete, inputs received in low intensity red light are adequate to drive the system.

The short-term (minute to minute) recovery mechanism is not a type of visual enhancement as visual feedback is not required during testing (e.g. Figure 7.11, VOR). The use of visual information is therefore *indirect* and it probably modifies circuitry used by the VOR, perhaps by temporarily increasing gain. This could be a form of rapid compensation similar to that used for adapting VOR gain when aging (15, 16) or when wearing various optical devices (17-23). This system starts to be effective immediately, but is not well-driven by low intensity red light.

Under normal conditions, these two mechanisms could operate independently but simultaneously. The short-term system would compensate within minutes for a sudden deficit, such as the effects of TR. The second mechanism would then slowly take over, perhaps to allow further rapid compensation to occur should an additional deficit develop.

OPTOKINETIC VERSUS PURSUIT SYSTEMS

Based on the neurophysiology of eye movements (see Chapter 2), it might be tempting to attribute the mechanisms presented above to

complementary contributions from the optokinetic and smooth pursuit systems. The effect of low intensity red light on these systems is hard to infer, however. In humans, there is no clear anatomical confinement of optokinetic processes to the peripheral retina and of smooth pursuit to the fovea (24-28). Furthermore, light intensity could have a significant effect, independent of color (29). Indeed, we have shown that gaze stability can be restored within tens of seconds if strong spectacles are put on (and later, taken off) in brighter red light. Neurophysiological explanations of our short and long-term mechanisms will therefore have to await further experimentation.

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The Cervico-Ocular Reflex Following Repeated Suppression of Vestibular Function.

INTRODUCTION

By using "Torso Rotation" (TR), we have shown that the overuse of simple reorienting movements can lead to significant changes in vestibular function (1 and Chapter 3). Repeated daily exposure to this technique leads to a gradual reorganization of sensory-motor integration, possibly involving a de-emphasis of vestibular signals as a reference (Chapter 4 and 5). After demonstrating that the gaze control system underwent long-term modifications following the same time course as adaptation to TR-induced motion sickness (Chapter 5), we wanted to identify *how* these long-term changes occurred.

At least five different neurophysiological systems can play a role in gaze control: the vestibulo-ocular reflex (VOR), smooth pursuit, the optokinetic system (OKS), the saccadic system, and the cervico-ocular reflex (COR). From previous experiments, we knew that the long-term reduction in gaze instability was not caused by the VOR becoming less sensitive to repeated exposure to TR or by an increased use of saccades (Chapter 4). We were therefore left with 3 systems, which could be divided into 2 "mechanisms": visual (smooth pursuit and OKS) and cervical (COR). Two experiments were designed and carried out simultaneously to identify which mechanism was being enhanced to compensate for the temporary vestibular problem. The role of vision was addressed in the previous Chapter. The role of the neck, and in particular the cervico-ocular reflex, will be presented here.

These results have appeared previously in abstract form (2).

METHODS

Six subjects performed this experiment in conjunction with "head-only" shaking in the dark, as described in the previous Chapter. All procedures were approved by the Research Ethics Board, Faculty of Medicine, McGill University.

TORSO ROTATION

TR consisted of reorienting gaze back and forth between 2 visual targets located 135° on either side of straight ahead. Combined movements of the eyes, head and torso were necessary to see the targets. This task was performed continuously for 30 minutes. Further descriptions of the technique have been published elsewhere (1 and Chapter 3).

CONTROLLED MOTOR ACTIVITY

To regulate the recovery from exposure to TR, subjects performed a series of controlled movements between tests. They were required to point their noses at one of 12 earth-fixed targets according to instructions given by a rapidly-paced cue tape (pseudo-random sequence). This task was performed daily during 2 separate 6 minute periods.

RED LIGHT

Precautions were taken to avoid large swings in EOG gain that would be expected following successive light / dark periods (3). Subjects were maintained under low intensity red light from 30 minutes prior to the beginning of data collection until the end of the experiment, 24 minutes after the completion of TR.

RECORDING EQUIPMENT

Data were acquired using a portable, custom-made digital data acquisition system described in the previous Chapter. Two rate sensors (Watson Industries) measured head and torso rotations, respectively. Eye position was measured using conventional electrooculography (DC-200 Hz). Data was stored on flash memory modules (White Technologies) for off-line analysis by computer.

NECK BRACE

The COR has been studied by recording eye movements generated during passive rotation of the trunk under a stationary head. However, there are limitations to this technique: i) the gain of the COR could be higher during voluntary movements than during passive rotations and ii) we were interested in movements requiring peak accelerations of the order of 2000°/s^2 (±15°, 2 Hz), posing safety problem. Additionally, it would be extremely difficult, if not impossible, to relax one's neck while being exposed to such a movement profile. Therefore, we took the opposite approach, eliminating neck movements by means of a modified orthopedic neck brace (USMC inc., Figure 8.1). Changes made did not affect the structural properties of the brace, but allowed it to be removed in a matter of seconds,should motion sickness develop (1 and Chapter 3).

"HEAD AND TORSO" SHAKING TEST

To perform these experiments, subjects wore the recording equipment and neck brace described above. Gaze stability without visual or neck inputs was evaluated during active "head and torso" shaking in the dark. Subjects were carefully instructed to shake their torsos at a fixed amplitude (about ±15°)

Figure 8.1 In addition to the portable data acquisition unit described previously (Chapter 7), subjects wore a modified orthopedic neck brace that prevented all head re torso movements.

while trying to maintain their gaze on an imagined, distant, earth-fixed target. They also had to constantly change the frequency of their torso movements, sweeping from 0.3 up to 3.0 Hz (if possible), guided by an auditory cue.

To prevent falls, particularly after TR, the experiment was carried out while standing inside a large steel drum that was bolted to the floor. In addition, subjects were monitored by an infra-red TV camera during the dark periods. Additional details are available elsewhere (Chapter 7).

TEST SCHEDULE

The experiment lasted 7 days. On each day, there were 4 test sessions (Figure 8.2): before TR ("BE"), immediately after TR ("IA"), 10 minutes after TR ("10") and 20 minutes after TR ("20"). During each of these sessions, 2 tests were performed in quick succession: "head and torso" shaking followed by "head-only" shaking, both in the dark. "Head and torso" shaking is the topic of this Chapter. "Head-only" shaking was already presented. EOG calibrations were obtained before, between and after these tests. Controlled motor activity was performed between the "IA" and "10", and "10" and "20" sessions.

DATA ANALYSIS

Signal processing and data analysis methods were identical to those used previously (Chapter 7). Unfortunately, unusual variability of subject movement made it impossible to look at gaze stability during EOG calibrations.

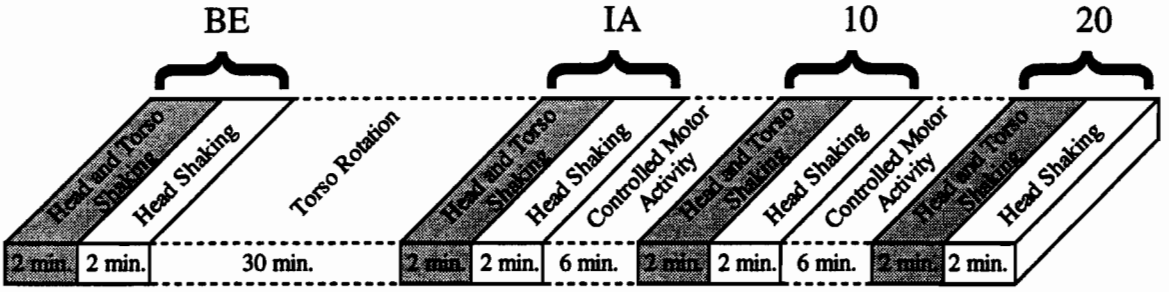

Figure 8.2 Daily test schedule. Data presented in this and the previous Chapter were acquired in quick succession. The sequence presented in this figure was repeated on 7 consecutive days. "Head and torso" shaking, as well as "head-only" shaking were performed in the dark. The rest of the time was spent in low intensity red light.

RESULTS

RAW DATA

Figure 8.3 is an example of the signals recovered from the recording equipment, after calibration, digital filtering and synchronization (see methods). The shape of the head velocity profile varied from almost sinusoidal at the higher frequencies to a wave form more closely resembling a square wave at the lower ones. Few saccades were seen and they were usually concentrated at the lower frequencies. Movement amplitude tended to be larger for "head and torso" than for "head-only" shaking and decreased with increasing frequency. This example may be compared with Figure 7.3 as both were taken from the same subject-session (Subject A, day 1 "BE").

VELOCITY GAIN

Figure 8.4 illustrates the velocity gain analysis method; instantaneous eye velocity has been plotted against instantaneous head velocity for a frequency bin covering the range 1.6 to 1.8 Hz (see Chapter 7). Data were taken from Subject A, day 1 "BE", the same session that was presented in the previous Figure and in Figure 7.4.

PHASE

The limitations described before for phase measurements also apply here. Since the intersample interval was 15.6 msec, any phase difference producing a shift smaller than or equal to this value cannot be measured with certainty. In almost every subject-session in the entire experiment, however, phase was within this range, and most often zero. We therefore consider phase to be 0°, within the time resolution limits of our analysis method.

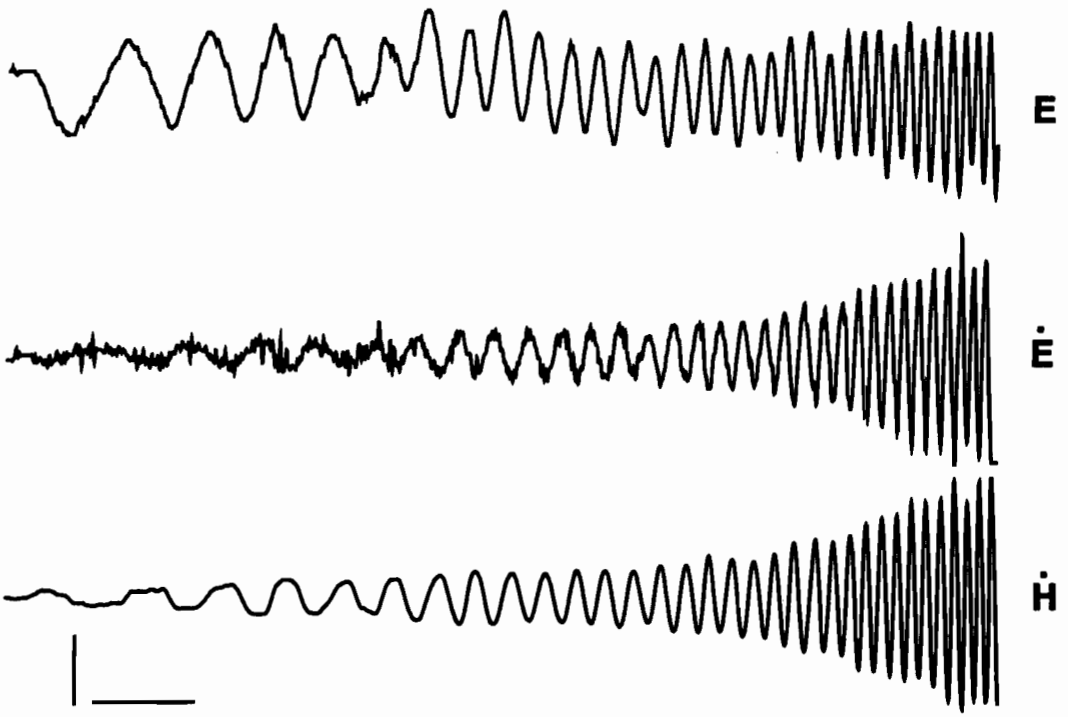

Figure 8.3 A complete "head and torso" shaking session before "Torso Rotation". Signals shown have been digitally filtered, undersampled at 64 samples/sec and synchronized. Illustrated are eye position (E), eye velocity ($\dot{E}$) and head velocity ($\dot{H}$). The vertical scale represents 20° for the position trace and 200°/sec for the velocity traces. The horizontal scale represents 4 seconds.

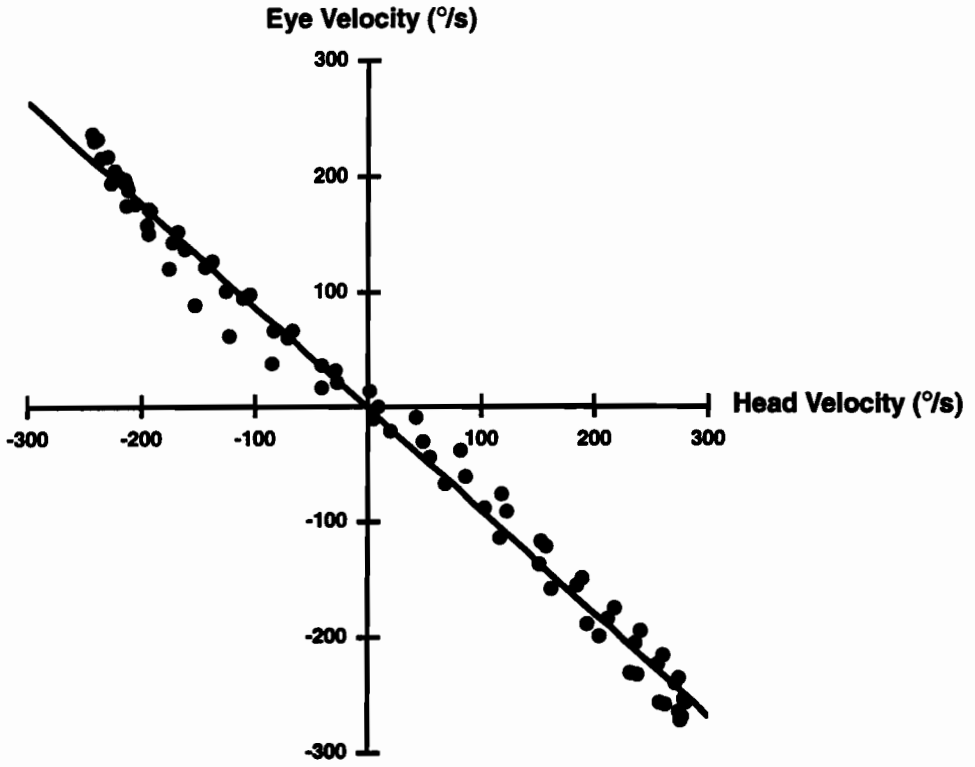

Figure 8.4 Velocity gain evaluation. For each frequency bin (in this case 1.6-1.8 Hz), instantaneous eye velocity was plotted against instantaneous head velocity. The slope of the linear fit (least squares method) defines the term "velocity gain". In this particular example taken from the previous figure, velocity gain is -0.89 (R^2 = 0.989). Phase shift, removed before the fit, was +9.6°.

FREQUENCY RESPONSE PLOTS

Once velocity gain was determined for all subject-sessions, frequency response plots were constructed. Data from subject E day 2 are shown in Figure 8.5. Before TR, velocity gain in the dark was close to unity at all frequencies (mean = 1.06). Immediately after TR, velocity gain was decreased at all frequencies (mean = 0.77). A small but significant ($P<0.05$) recovery was seen in the 20 minutes following TR, when comparing averages of all days "IA" to either "10" or "20" averages (Figure 8.8).

GROUP SUMMARY

Figure 8.6 summarizes the results obtained in our 6 subjects over 7 days. The range of frequencies over which all subjects could perform acceptable "head and torso" shaking was limited to 0.6 - 1.4 Hz. Each day immediately after TR, gaze stability in the dark was reduced. The decline only reached statistical significance on 5 days, however (* $P<0.05$, paired t-test).

COMPARISON TO HEAD-ONLY SHAKING IN THE DARK

In Figure 8.7, combined results from "head-only" and "head and torso" shaking have been superimposed. Data have been taken from day 4 and are the mean of all 6 subjects. Before TR, "head-only" velocity gain was somewhat lower than "head and torso". After TR, the opposite was true. The shapes of the curves are similar under both testing conditions.

THE ROLE OF THE CERVICO-OCULAR REFLEX

By comparing "head and torso" shaking results to those obtained during "head-only" shaking, we can estimate the contribution of neck inputs

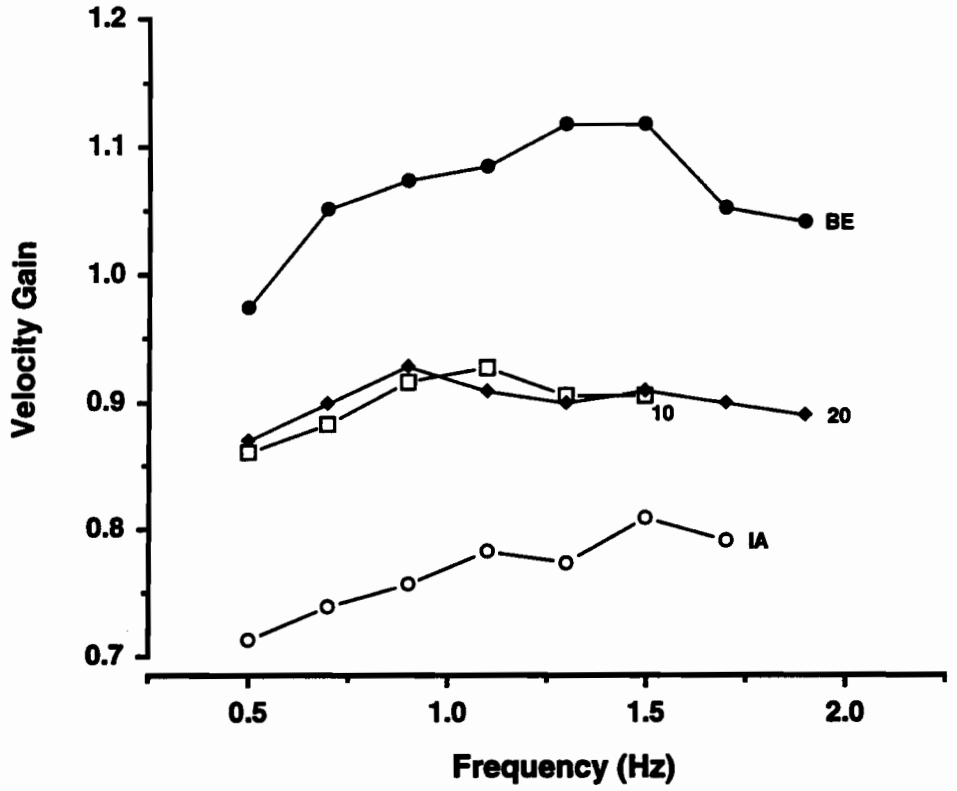

Figure 8.5 Frequency response curves for the four daily tests in one subject. Before TR ("BE"), velocity gain was close to unity at all frequencies, i.e. image slip was minimal. Immediately after TR ("IA"), the gain was reduced across all frequencies tested. Phase, not shown, was almost always less than our time resolution limit. Gaze stability was not back to normal 20 minutes after TR ("20").

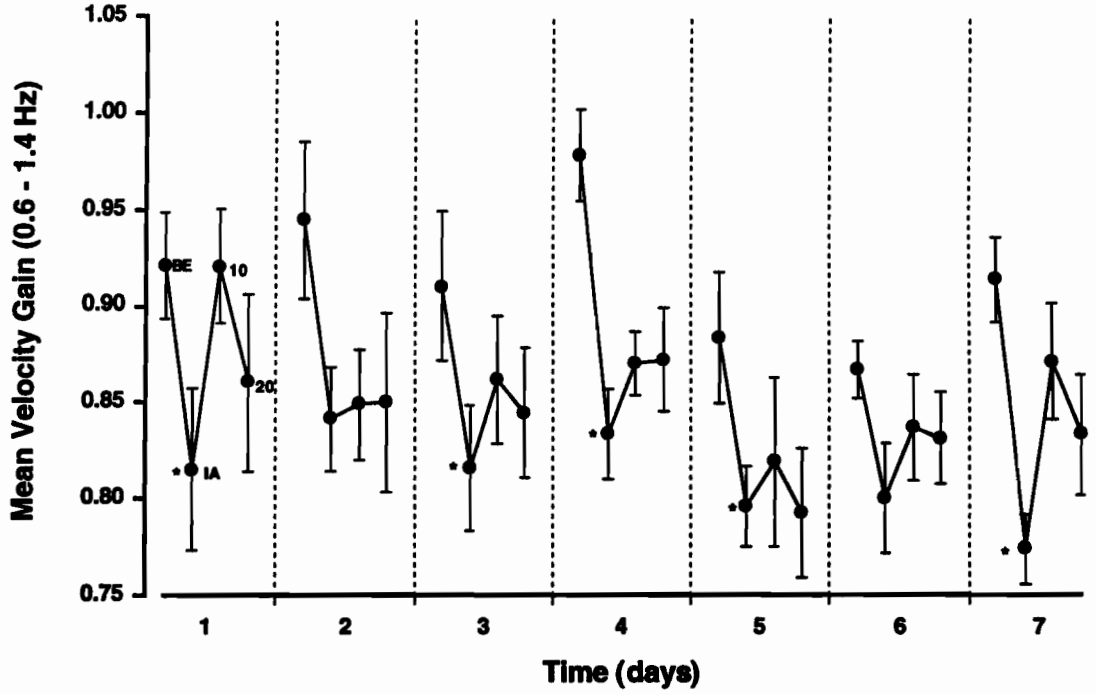

Figure 8.6 Effects of repeated exposure to TR on group mean velocity gain in the dark. Each point represents the average velocity gain ± 1 standard error for 6 subjects, over the range where all could perform acceptable "head and torso" shaking (0.6-1.4 Hz). Velocity gain was decreased immediately after TR. The difficulty of maintaining a clear mental image of the target during the test augmented data scatter, and a significant drop in gain was only measured on 5 of the 7 days (* $P<0.05$, paired t-test). Gaze stability did not return to normal in the 20 minutes following Torso Rotation.

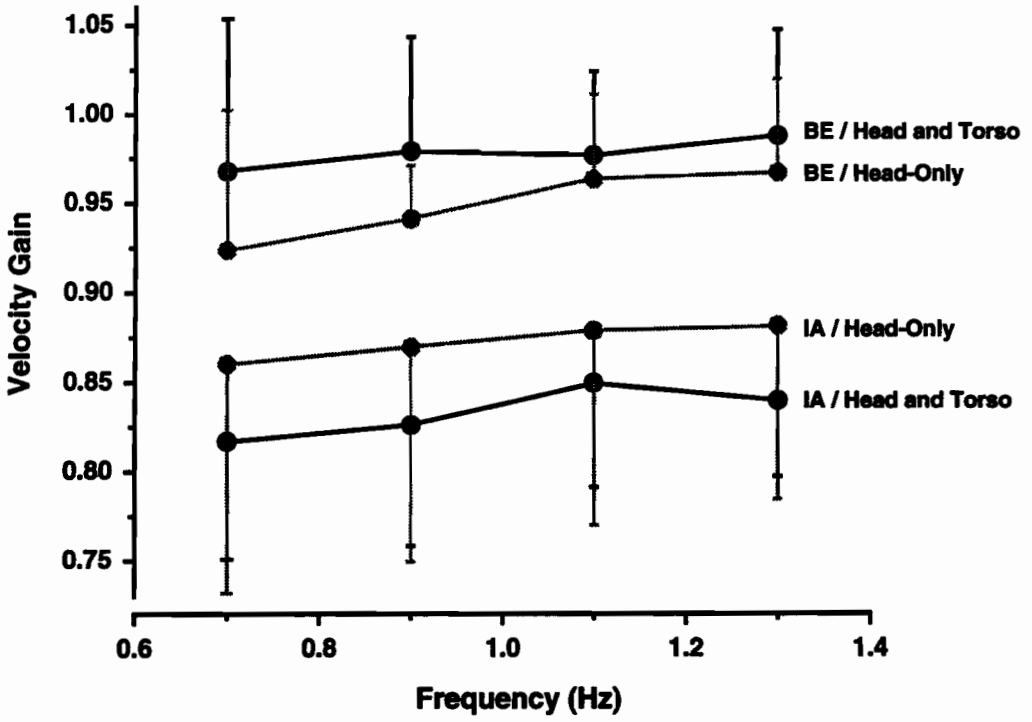

Figure 8.7 Comparison between "head-only" (grey circles) and "head and torso" (black circles) shaking in the dark. These data represent the mean (± S.D.) across all 6 subjects on day 4. The results for "head-only" and "head and torso" shaking are surprisingly similar.

to gaze stability. This is summarized in Figure 8.8, in which each point is the overall average for 6 subjects tested on 7 consecutive days. Using paired statistics, only the "IA" points were different from each other ($P<0.01$). Mean velocity gain measured during "head and torso" shaking also showed a small but significant recovery ($P<0.05$) during the 20 minutes after TR.

DISCUSSION

THE ROLE OF THE CERVICO-OCULAR REFLEX

This experiment complements the previous study (Chapter 7), the only significant difference being the use of a tight-fitting neck brace that required the subject to rotate the head *and* torso as a unit. The purpose was to eliminate proprioceptive cues underlying the COR in addition to eliminating visual inputs. The results obtained were very similar to those produced by head-only shaking in the dark. In the absence of both of these sources of information during testing, there was no day-to-day recovery of gaze stability. Nevertheless, subjects did note that after a few days it was much easier to keep their eyes on target while doing calibrations in low intensity red light, even with the brace in position. Additionally, controlled motor activity with the brace off and in low intensity red light produced very little short-term (within 20 minutes) recovery.

These findings confirm the fundamental importance of vision for both rapid compensation and longer-term, day-to-day recovery of gaze stability following TR-induced vestibular suppression. In contrast, it would appear that the COR plays little if any role. This is not surprising when vestibular function is still normal (4-7), but even when adaptation is not only necessary but even happening, the COR still does not contribute.

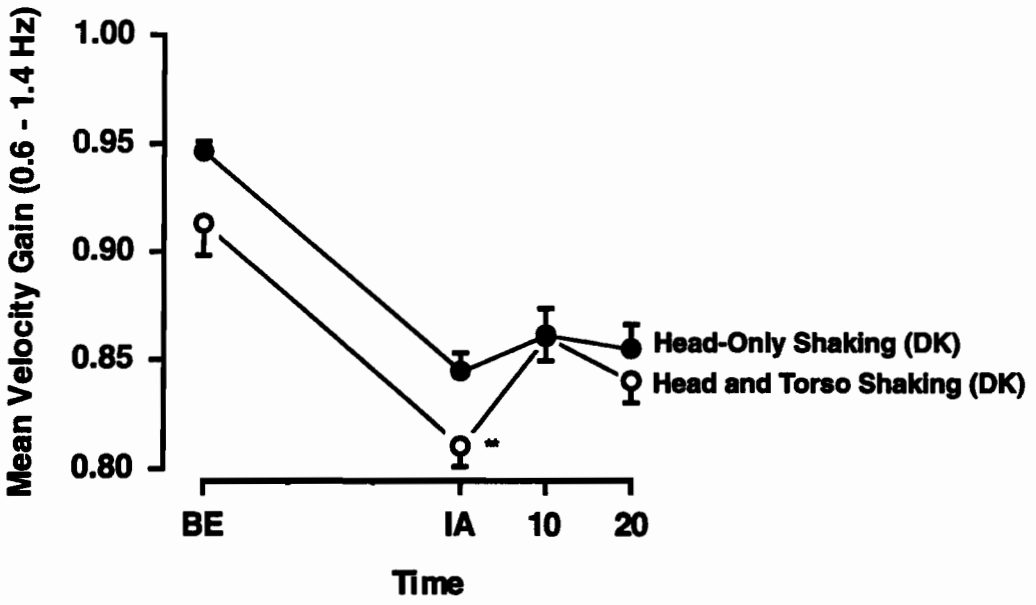

Figure 8.8 Summary of "head-only" (●) and "head and torso" (○) shaking experiments. Each point is the mean of 7 days of testing. Only the "IA" points are statistically different from each other (**P<0.01).

An "enhanced" COR has been reported in vestibular patients (8-10), but the frequency and velocity response characteristics of that reflex should be considered. Significant COR contributions are only seen below 0.3 to 0.4 Hz (10) and they are maximal with stimuli in the 4 to 9°/sec range (11). Normal head movements have a frequency content of 0.1 to 5.0 Hz (4, 12, 13) and include velocities well in excess of 100°/sec. In this experiment, successful testing was restricted to 0.6 to 1.4 Hz, comparable to normal movements. While we cannot eliminate the possibility that COR gain increased below 0.6 Hz only, it is hard to imagine why this would occur, since visual tracking is effective in that range but not so useful at higher frequencies.

CHANGES IN GAZE STABILITY AFTER TORSO ROTATION

Several experiments have now examined the effects of TR on gaze stability and the evidence suggests that more than one mechanism is probably involved. The following brings together what is known and what is suspected concerning these mechanisms. The conceptual diagram presented in Figure 8.9 attempts to summarize these points and should not be considered a model in the formal sense. Similar diagrams could probably be constructed for the postural, perceptual and motion sickness systems, but these are not considered here.

To begin, Figure 8.9 includes a simple pathway with a semicircular canal as a representative source of vestibular signals, a box that controls how effective these signals will be at producing reflex eye movements, a point at which visually-originating signals can be added and an appropriate extraocular muscle attached to an eyeball. Added to this is a second path that takes image slip signals from the retina and feeds them back to the first path at two different points. In the first case, after going through a box that

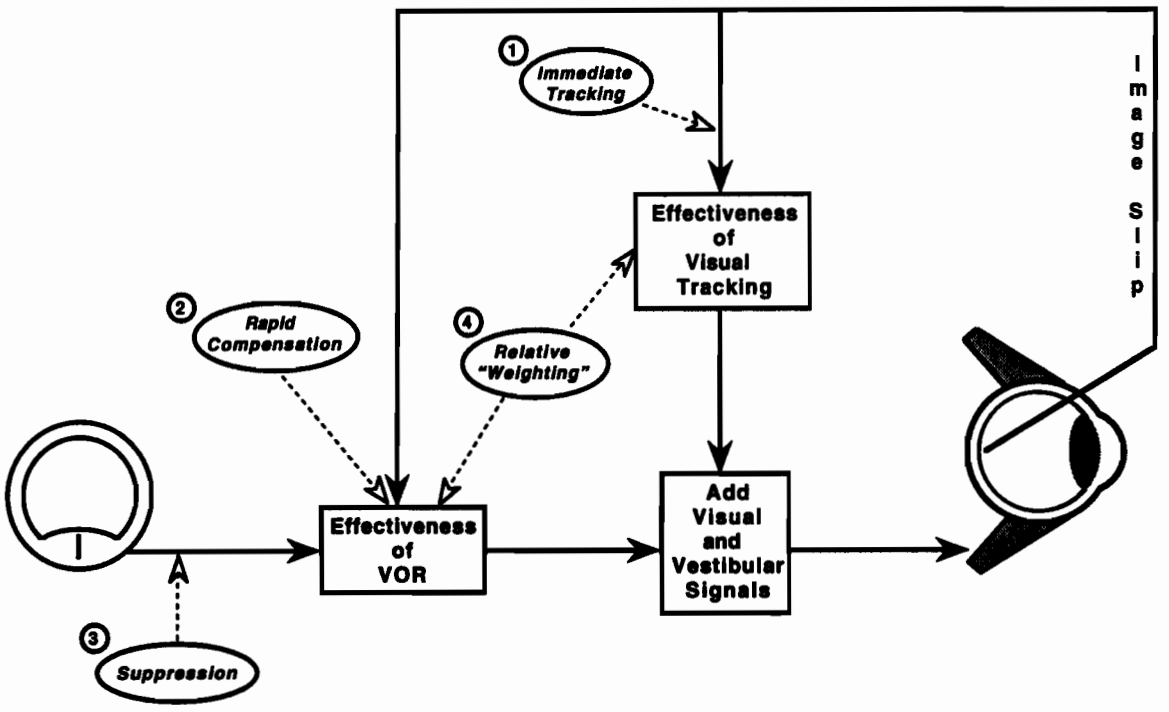

Figure 8.9 Summary diagram of four different mechanisms that may combine to produce the effects seen in these experiments and how they may interact. Details may be found in the Discussion section of this Chapter.

controls how effective these signals will be, they become the visually-originating signals referred to above. In the second case, they go back to the box controlling VOR effectiveness. In other words, the first path mediates visual tracking and the second, plastic adaptation of the VOR. Also included in Figure 8.9 are suggestions of four different mechanisms, each acting over a different time scale, that are presumed to affect gaze stability during and after TR.

The fastest means of correcting for image slip after TR is to use the pursuit and optokinetic systems, with saccades if necessary. This has been termed "immediate tracking" and is most effective at lower frequencies of head movement (Figure 5.4). The use of this mechanism is unrelated to the development of motion sickness. Controlled motor activity (CMA) immediately after TR is equally effective at generating symptoms if the eyes are open or closed. Conversely, if the eyes are kept closed during 20 minutes of CMA immediately after TR and then opened, the significant gaze instability that is present at that time is not provocative.

The second mechanism requires a few tens of minutes to become effective. Termed "rapid compensation", it may also be used to correct for aging (14) or the use of various optical devices (15-18). It acts by modifying the effectiveness of the circuitry used by the VOR and does not require further visual inputs once complete. It may be related to motion sickness, because susceptibility drops dramatically as rapid compensation occurs. However, symptoms may develop hours later. Furthermore, symptoms do not occur after repeated exposure to TR, even though rapid compensation takes place on a daily basis. Therefore, the apparent relationship may only be coincidental.

The third mechanism is highly speculative. We do not know how or where TR changes neural function, nor do we fully understand how these changes may interact with the various means of compensation. "Suppression" affects all aspects of vestibular function at the same time, including gaze control, postural control and perception of motion (Chapter 3). It modifies the VOR even in the absence of visual feedback (Chapter 3). Indeed, retinal image slip during TR would tend to increase VOR gain, but the reverse occurs. It may be responsible for the lack of motion sickness symptoms *during* TR. For a given duration of TR, the amount of suppression is always the same (e.g. VOR gain is reduced by the same amount, Chapter 3). Prolonged exposure results in more profound effects (Chapter 3). TR-induced suppression occurs uniformly *across all frequencies* (Chapter 7) as opposed to prism-induced changes that tend to be *frequency-dependent* (17, 19). Complete recovery seems to take hours, as demonstrated by the late occurrence of motion sickness symptoms as well as postural, locomotor and gaze control errors. Finally, suppression recovers spontaneously, independent of visual image slip, with approximatively 75-80% recovery in 6 hours (Chapter 3). In contrast, prism-induced plastic adaptation is stable in the absence of vision, even over-night (16).

The fourth and final mechanism becomes active only after repeated exposure to TR. Termed "relative weighting", it implies a change in sensori-motor strategy that includes less reliance on a vestibular reference and more on other sensory inputs, especially vision in this case. Similar changes have been demonstrated in response to vestibular lesions (20). Previous experiments in this series demonstrated that the time course of this process is similar to that of the decrease in motion sickness susceptibility caused by repeated exposure to TR (Chapter 5). This does not necessarily imply

causality (decreased gaze slip does not cause decreased motion sickness) but it does suggest there may be some common underlying mechanism. Perhaps repeated "suppression" of vestibular inputs leads to *both* (a) a relative increase in the use of visual inputs to acheive gaze stability and (b) a relative decrease in the ability of abnormal vestibular signals to cause motion sickness. The latter would lead to a general, transferable type of adaptation to motion sickness, quite different from the specific, non-transferable protection that can also be produced, as explained by Reason's model (21).

In summary, we propose that torso rotation acts by suppressing "vestibular inputs", one consequence being gaze instability. Immediately, visual tracking driven by retinal image slip attempts to correct but is only partly effective. Within tens of minutes, image slip also causes a rapid, compensatory increase of VOR gain, which succeeds in restoring gaze stability. As the suppression of "vestibular inputs" gradually disappears over a period of hours, less and less rapid compensation is required. However, as a result of this exercise, the VOR becomes a little less important, and vision a bit more important, as a reference signal for maintaining gaze stability. At the same time, the individual becomes less prone to motion sickness. Further experiments will be required to understand and exploit this relationship.

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Contribution to Original Knowledge.

As required by the Faculty of Graduate Studies and Research of McGill University, the following are considered to be the main contributions to original knowledge made by this thesis:

1) "Torso Rotation" produces widespread changes in vestibular function.

2) Active movement performed immediately after "Torso Rotation" causes postural and gaze instability, perceptual illusions and motion sickness.

3) With repeated exposure to "Torso Rotation", motion sickness gradually disappears.

4) Gaze instability immediately after "Torso Rotation" also improves, along a time course that is closely similar to that of the loss of motion sickness symptoms.

5) This improvement *is not* due to changes in the vestibulo-ocular reflex, cervico-ocular reflex, or predictive mechanisms.

6) It *is* due to increased use of a visual reference.

7) While the improvement in gaze stability *is not* directly responsible for the decreased susceptibility to motion sickness, it is proposed that these two changes reflect a common underlying mechanism, involving a de-emphasis of vestibular inputs and increased use of other sensory modalities.

8) This should lead to a generalized, transferable type of adaptation, quite different from but complementing the more commonly studied specific, non-transferable type.

9) Indeed, during the course of these experiments, susceptibility of our subjects to other, quite different provocative environments also decreased.

10) A descriptive model has been developed suggesting that "Torso Rotation"-induced suppression is a new and separate mechanism that may drive this form of adaptation.

11) This mechanism might be more accessible to pharmacological intervention, perhaps even a means of chemically pre-adapting susceptible individuals.
